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DISEASES OF CHILDREN

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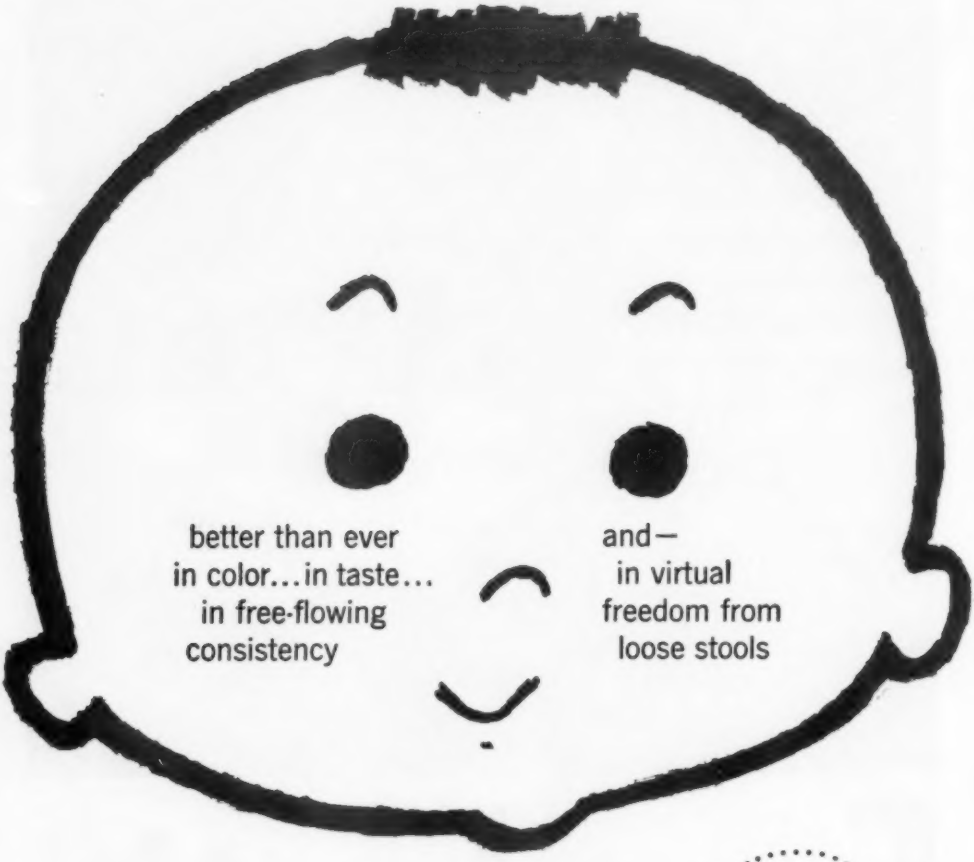

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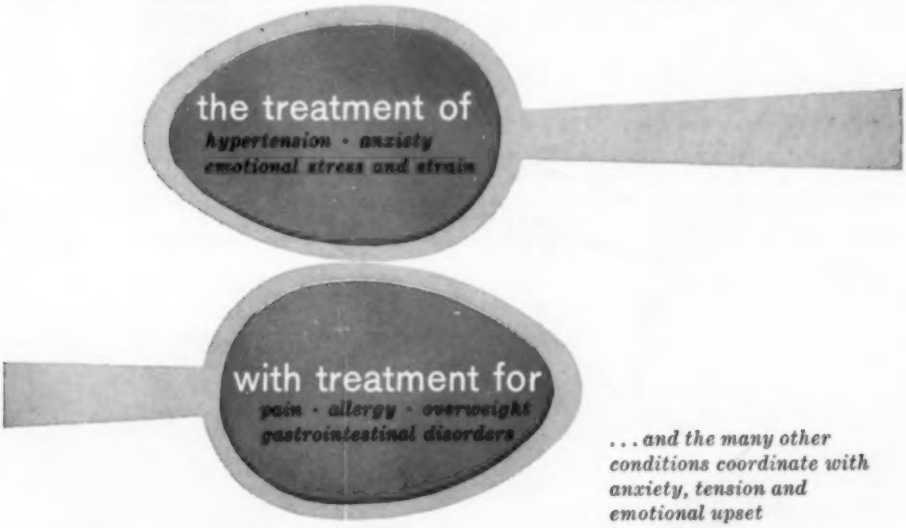

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A.M.A. Journal OF
DISEASES of CHILDREN

Organic Behavior Disorder

Behavior Characteristics of Brain-Damaged Children

DORIS H. MILMAN, M.D., Brooklyn

The subject of this study is the clinical investigation of a state which is known variously as organic brain disease (Bender [1]), organic drivenness (Kahn and Cohen [2]), brain injury (Strauss [3]), organic state (Silver [4]), and minimal cerebral injury (Gesell [5]).

The definition of Strauss and Lehtinen is most apt in its specificity and inclusiveness for delineating the subject of this investigation. These authors define a brain-damaged child as "one who before, during, or after birth has received an injury to or an infection of the brain. As a result of such organic impairment, defects of the neuromotor system may be present or absent; however, such a child may show disturbances in perception, thinking, and emotional behavior, either separately or in combination." The damage referred to may be the result of trauma, hemorrhage, infection, toxic agents, or anoxia and can conceivably occur at any stage in the life cycle, from the time of uterine implantation through postnatal existence. Such a lesion may be mild or severe, localized or diffuse. It may vary from minimal cytological impairment to gross destruction of tissue and can include the pathological entities of scarring, meningeal adhesions, gliosis, vascular occlusion, necrosis, atrophy, and hemorrhage.

Received for publication Jan. 5, 1956.

Division of Pediatric Psychiatry, Jewish Hospital of Brooklyn.

The functional consequences of such damage depend upon the location, the extent, and the level of maturation of the organism at the time the damage occurred. Pasamanick and Lilienfeld [6] have added greatly to present knowledge by their epidemiological studies of the association of prenatal and paranatal factors with the occurrence of behavior disorders, mental deficiency, and other expressions of central nervous system impairment. They underline the common denominator that exists among the variety of etiological agents and anatomical sites of damage by referring to a continuum of pathology varying from one extreme of prenatal death of the fetus to the other extreme of minimal impairment of motor or intellectual or behavioral function.

It is at the minimal extreme of the continuum of brain damage that a clinical syndrome can be defined, this despite the diversity of etiological, anatomical, and pathological possibilities. It is postulated that a minimal lesion, whether localized or diffuse, so impairs the integrity of the functioning whole that a syndrome of minimal impairment can be recognized. Silver [4] defines this syndrome as "defects in motor performance seen in patterned or reflex behavior; perceptual defects; emotional response underlined by frustration and anxiety." Bender,[1] too, points out the "difficulties in patterned behavior in motor, perceptual and emotional-social areas with a tendency to regressed or retarded maturation" and emphasizes the occurrence of severe and poorly patterned anxiety. Bakwin and Bakwin [7] summarize the behavioral characteristics more specifically as those of

hyperkinesis, excessive clinging, attention-seeking, lability of mood, explosive and unprovoked anger, impulsivity, destructiveness, distractibility, variability in memory, and anxiety in response to antigravity play. Strauss and Lehtinen [3] underline the emotional explosiveness, the distractibility, the difficulties in perceptual and conceptual thinking which result in bizarreness, and the disintegration in perceptual-motor coordination. Gesell [5] notes the frequent association of reading disability and speech defects with minimal brain injury.

The present study is a review of 22 brain-injured children who were encountered in a child guidance clinic. The study was undertaken retrospectively for the purpose of validating the thesis that a clinically recognizable syndrome exists and to gather quantitative data with respect to the various components of the syndrome. The present 22 cases were encountered as routine admissions to the clinic among a total of 200 cases admitted over a five-year period.

Table 1 shows the source of referral of the cases. Thirteen children were referred by medical sources, including private physicians and psychiatrists, pediatric clinics, rehabilitation clinics, and psychiatric clinics. Eight children came from nonmedical sources, seven from schools and one from a recreational group.

TABLE 1.—*Source of Referral of Patients*

Source	Patients, No.
Medical source	13
Pediatric clinic	5
Rehabilitation clinic	2
Private physician	2
Private psychiatrist	2
Psychiatric clinic	1
School	7
Recreational group	1
No record	1

TABLE 2.—*Age at Time of Referral*

Age at Nearest Birthday, Yr.	Patients, No.
6	2
7	4
8	2
9	8
10	1
11	2
12	0
13	2
14	1

TABLE 3.—*Neurological Diagnosis*

Diagnosis	Patients, No.
Chronic brain syndrome	15
Chronic convulsive disorder	3
Cerebral palsy	3
Arrested hydrocephalus	1

TABLE 4.—*Etiology*

Etiology	Patients, No.
Unknown	8
Inflammatory encephalopathy	4
Erythroblastosis fetalis	3
Prematurity	3
Birth injury	2
Attempted abortion	1
Antepartum bleeding and drug addiction	1

The age at the time of entrance to the clinic (Table 2) ranged from 5 years 6 months to 13 years 10 months. Sixteen children, or 73% of the total, were between the ages of 6 and 10, the period corresponding to the appearance and recognition of learning difficulties in school.

A neurological diagnosis was made in each case on the basis of history and clinical and laboratory data. It will be seen from Table 3 that the cases fall into four categories. The largest number of cases, 15, falls into the category of chronic brain syndrome of unclassified type. The diagnosis was based upon one or more of the following findings: history of antepartum or intrapartum trauma or exposure to toxic agents, abnormal neurological signs, abnormal electroencephalogram. Three cases were diagnosed as chronic convulsive disorder; three were mild but definite cases of cerebral palsy, and one child had an arrested hydrocephalus.

When the cases were analyzed with respect to etiology (Table 4) it was observed that the largest single category, eight cases, was of unknown etiology. Seven of these were cases designated as chronic brain syndrome, and one was idiopathic epilepsy. The next largest etiological group was that of inflammatory encephalopathy, wherein measles accounted for two cases, pertussis for one case, and nephrosis with multiple febrile episodes and prolonged cerebral edema for one case. There

were three cases of neonatal jaundice due to erythroblastosis fetalis. Two of these children had the characteristic choreoathetoid cerebral palsy and pitch cut-off deafness which is known to be associated with kernicterus. Prematurity accounted for three cases, and birth trauma in full-term infants accounted for two more. There was one product of attempted abortion and one product of antepartum bleeding and maternal barbiturate addiction.

The significant medical findings are recorded in Table 5. Nine children in the group were outstandingly thin, pale, and poorly nourished. There were six instances of narrowing or flattening of the vault of the cranium. Four children had strabismus or refractive error or both. Three children had a clinically significant hearing loss. With the exception of the cases of Guillain-Barré disease and rheumatoid arthritis, all the pathological conditions, both those that involve the central nervous system and those that do not, represent either congenital or constitutional defects or are related to birth trauma.

TABLE 5.—*Significant Medical Findings*

Pathological Condition	Patients, No.
Poor nutrition	9
Decreased size of cranial vault	6
Eye defects	4
Hearing loss	3
Obesity	2
Hydrocephalus	1
Undescended testicle	1
Spina bifida occulta	1
Hirsutism	1
Hypothyroidism	1
Inguinal hernia	1
Persistent branchial cleft	1
Clubbed feet	1
Rheumatoid arthritis	1
Guillain-Barré disease	1

TABLE 6.—*Significant Neurological Findings*

Neurological Signs	Patients, No.
Impairment of fine coordination	11
Tremors, choreoathetotic movements	8
Disturbed gait (infantile, awkward, ataxic)	7
Crossed laterality	4
Whirling	4
Difficulty in eye convergence	4
Finger-to-nose ataxia	4
Absence of associated arm movements	4
Impairment of gross coordination	4
Impairment of balance, positive Romberg test	4
Dysdiadochokinesis	2
Left central facial palsy	1
Impaired sensation in lower extremities	1
Drooling	1
Weakness of fingers	1
Babinski reflex positive	1
Nystagmus	1
No abnormal signs	3

TABLE 7.—*Speech Defects*

Type of Defect	Patients, No.
Slurring	12
Disturbance of rhythm	4
Substitute consonant sounds	5

The most frequently encountered neurological abnormality was impairment of fine coordination (Table 6). This was noted in 11 cases. Eight children exhibited tremors or choreoathetotic movements. A gait disturbance was recorded in seven instances. Fourteen other major and minor neurological signs were noted with the frequencies indicated in Table 6. In three children no abnormal neurological signs were elicited, but these children were not subjected to repeated examination.

Speech was impaired in 13 children and clear in 8 children, and there was no record in 1 case. Table 7 indicates the type and frequency of speech disorders. Twelve children had slurred or poorly articulated speech, and one had slow and hesitant speech. There were four instances of disturbance in speech rhythm, including stammer, explosiveness, and hesitation. Five children retained infantile substitute sounds. Of 7 children in the group of 22 who had a history of delayed speech development, only 1 subsequently developed clear, normal speech pattern.

Psychological data were obtained from the administration of one or more of the following tests: Stanford-Binet, Wechsler Bellevue, Bender Gestalt, Wide Range Achievement, Rorschach, and Children's Apperception Test. Intelligence quotients (Table 8) ranged from 70 to 118. Seventeen children rated a score between 80 and 100, with three cases below and one above these levels. Thus, applying current interpretations of I. Q. scores, this can be considered a group of children of "normal" or "low normal" intelligence with three "borderline" cases. Psychological abnormalities were more apparent in specific

TABLE 8.—*Intelligence Quotients*

I. Q. Range	Patients, No.
70 through 79	3
80 through 89	8
90 through 99	9
100 through 109	0
110 through 119	1
No record	1

TABLE 9.—*Psychological Test Findings*

Test Finding	Patients, No.
Visual-motor incoordination	15
Impairment of rote memory or recall	7
Uneven functioning, wide scatter	6
Poor perceptual organization	5
Discrepancy between verbal and performance scores, poor performance, poor manipulation	5
Vocabulary score higher than mental age	4
Impairment in reasoning, conceptualization, use of symbols	2

TABLE 10.—*Reading Ability*

Reading Level	Patients, No.
Average	2
Retarded or nonreader	16
No record or below reading age	4

areas of mental functioning than were revealed by the crude I. Q. scores. A significant degree of visual-motor incoordination was recorded 15 times. The next most frequent defect was impairment of rote memory and recall. Performance was uneven in six instances, with failures on simpler tests and successes on more difficult tests. Poor perceptual organization was noted in five cases. Five children were more facile in verbal than in manipulative performance. Other deviations can be seen in Table 9.

An analysis of reading ability (Table 10), the prerequisites for which are speech and language facility, intelligence, visual-motor coordination, rote memory, and perceptual organization, points up the handicapping nature of the psychological impairment. On the basis of intelligence quotient alone one would anticipate that half the group or more would find average success in reading. Yet only 2 out of 22 children had average reading skill for their age. Sixteen were retarded in reading or were totally unable to read. In four cases the children were too young to be considered or there was no record of reading ability. Five children exhibited mirror reading and/or reversal of letters or words. In those cases where the grade level was known, five children were retarded two years in reading, two were retarded three years, one was retarded five years, and one was retarded six years.

The behavior characteristics of this group of brain-damaged children were reviewed from four different aspects: presenting complaint, observed behavior, neurotic traits, and social adjustment. Table 11 lists the mother's presenting complaint or the reason given for referral to this clinic. Poor progress in school, alone (once) or in combination with other complaints, accounted for 12 referrals. Disobedience was the presenting problem in six instances. Fifteen other symptoms or traits were offered as the presenting problem or problems. The number and variety of these complaints was in sharp contrast to the uniformity of behavior that was revealed in the further analysis of these records. The diversity (except for school problems and disobedience) of presenting complaints probably reflected parental bewilderment and inability to pin-point the disorder rather than any great variation among the children themselves.

Behavior traits (Table 12) were compiled from the parents' histories and the clinical

TABLE 11.—*Presenting Complaints*

Complaint	Patients, No.
Poor progress in school	12
Disobedience	6
Impaired speech	3
Stealing	2
Social inadequacy	2
Tics	1
Enuresis and drooling	1
Restlessness	1
Nervousness	1
"Psychosomatic" limp	1
Quarreling	1
Sexual awareness	1
Compulsion	1
Aberrant development	1
Day-dreaming	1
Obesity	1
Tantrums	1

TABLE 12.—*Behavior Traits*

Traits	Patients, No.
Restlessness, hyperactivity, impulsiveness	12
Negativity, quarreling, nonconformance	11
Inattention, distractibility	10
Teasing, aggression, destructiveness	8
Fearfulness	6
Tantrums	5
Day-dreaming, seclusiveness	5
Excessive masturbation	5
Mischievousness, unruliness, disobedience	4
Lying, stealing	4
Immaturity, excessive dependency	4
Sensitivity, suspiciousness, hatefulness	4
Regressive behavior (enuresis, thumb-sucking)	4
Bizarreness (talking to self, compulsions)	2
Apathy, lethargy	2

TABLE 13.—*Personality Traits*

Traits	Patients, No.
Tension, anxiety, depression	17
Negativity, hostility, aggression	13
Insecurity, inadequacy, inferiority, rejection	12
Immaturity, dependency, regression	12
Shyness, withdrawal, constriction, detachment	9
Fearfulness	6
Suspiciousness	6
Inhibition, blunting, repression	5
Rigidity	2
Passivity	2
Excessive fantasy	1

observations of psychiatrist, psychologist, neurologist, pediatrician, and reading therapist. Each category lists related traits in order of increasing severity. Hyperacitivity, which varied from mild restlessness to ceaseless roaming and running, was noted in 12 children. Varying but significant degrees of negativity occurred in 11 children. Distractibility, aggression, and fear were frequently observed. Other traits occurred less prominently, with frequencies as indicated in Table 12.

A study of personality structure by means of psychiatric interviews and projective tests (Rorschach and Children's Apperception Test) shed additional light on the emotional life of these children and revealed even greater uniformity than the observation of behavior traits. Again, in Table 13 related traits are grouped together in order of increasing severity. The outstanding finding, in 17 out of 22 children, was that of tension, anxiety, or depression. Negativism or aggression was evident in 13. Feelings of inadequacy and rejection were present in 12 children. Immaturity, dependency, and regressive trends were equally common. A significant number of children showed varying degrees of emotional constriction, fearfulness, suspiciousness, and ideas of persecution. It is noteworthy that the trait of excessive fantasy, so common in neurotic and schizophrenic children, occurred in only one case in this series. On the contrary, the inner life of these children was characterized by emptiness, inhibition, negativism, and feelings of inadequacy and frustration.

A study of social adjustment further highlighted the inadequacies of the brain-damaged child. Eighteen children (Table 14) had a poor social adjustment with few or no friends and inability to relate to peer groups. Only four were said to have normal relationships with peers. Eleven children were physically aggressive. Five showed extreme degrees of sibling rivalry. Three were able to play only with younger children.

The school record (Table 15) was considered to be the final resultant of all the impaired forces (physical, neurological, psychological, behavioral, emotional) that a child brings to bear on this, his ultimate test of success in childhood. Of 21 children of grade-school age, 20 children in this series had an unsatisfactory school record and one had a satisfactory record. Seven children were placed in special classes for slow learners, nonlearners, or physically handicapped. As might be expected, the attitude toward school was poor in many instances: inattentiveness in eight, unmotivated in six, and unruly in three.

TABLE 14.—*Social Adjustment*

Type of Adjustment	Patients, No.
Poor: few friends or no friends	18
Normal peer relationships	4
Social Behavior	
Aggressive	11
Sibling rivalry	5
Regressive: plays only with younger children	3
Afraid of children	1

Parental attitudes, although in no sense the determinants of the deviant behavior patterns, are significant in revealing the negative effect upon parents of rearing exceptional children. In this series (Table 16) varying degrees of disapprobation were recorded 12 times, varying degrees of ambivalence or rejection 11 times, and anxiety 9 times. Only three mothers were observed to be warm, sensitive, and sympathetic, although five were solicitous and highly protective.

TABLE 15.—*School Record*

Type of Progress	Patients, No.
Poor	20
Satisfactory	1
Too young to be evaluated	1
Type of Class Placement	
Regular class	15
Health improvement class	3
Special opportunity class	3
Retarded children's class	1
Attitude Toward School	
Inattentive	8
Unmotivated	6
Unruly	3

TABLE 16.—*Parental Attitudes*

Attitude	Patients, No.
Disapproving, threatening, punitive	12
Ambivalent, resentful, rejecting	11
Unhappy, anxious, guilty, despairing	9
Solicitous, protective	5
Baffled, bewildered	4
Warm, sensitive, sympathetic	3

TABLE 17.—*Results of Treatment*

Result	Patients, No.
Marked improvement	4
Improvement	10
No improvement	5

The results of treatment are recorded in Table 17. Treatment consisted of one or more of the following modalities: psychotherapy, parental guidance, remedial tutoring, music therapy, drug therapy. Of 19 children who received treatment for periods of time varying from 6 months to 2 years, 14 were significantly improved and 5 were unimproved. Improvement took the form of better social adjustment, better conformance, greater acceptance of self, more positive and realistic goals.

COMMENT

The foregoing data clearly reaffirm the thesis of other observers that minimal degrees of brain damage have clear-cut and recognizable consequences in respect to these critical areas of development and functioning: motor patterning; visual-motor coordination and perception; language, including speech and reading; behavior patterning; personality, and social relationships. The deviations are sufficiently uniform and consistent to constitute a syndrome, which can be designated organic brain disorder. The etiology can almost always be found in the hazards of ontogeny or birth or in the childhood infectious diseases, to which the immature central nervous system is so peculiarly vulnerable. The neurological consequences, where damage has been minimal, are usually subtle, and signs of impairment are not elicitable by ordinary clinical means. Only tests of the highest motor integrative functions (such as fine coordination, postural tone and stasis, homolateral eye and hand dominance, and maturity of gait with mature associated movements) are likely to show impairment. Intelligence tends to be average, where the damage has not been great enough to produce retardation. However, intelligence rarely reaches higher than average levels (by conventional tests) because of the impairment of specific psychological functions which intelligence tests measure. The psychological function which is most vulnerable is that of visual-motor coordination, with rote memory, perceptual organization, reasoning, conceptual thinking, and use of symbols also being compromised. It may be that brain-injured children occasionally reach higher levels of intelligence than these studies show and that such children compensate for their deficiencies by virtue of their superior intelligence, thereby escaping the attentions of a child guidance clinic. However, children of average or low average intelligence and minimal brain damage come into their social milieu with the aforementioned neurological and psychological deficits and few if any compensatory mechanisms. They encounter repeated

defeats and frustrations in the acquisition of motor skills, in the orientation of their bodies in space, in the perceiving of themselves as comprehensible whole persons. They have difficulties in speech which limit their social effectiveness. Thus their opportunities for failure are many. Their behavior traits of hyperactivity and nonconformance and distractibility render them still more unacceptable and open to rebuff. Whether these behavior traits are due to failure of cortical inhibition or are due to fluctuations in perception between figure and background (Strauss [3]) or are due to a compulsive need to compensate for unsatisfying orientation and spatial perceptions (Bender [1]), the social consequences of the behavior are the same: failure and ostracism. Personality development, in turn, suffers from the consequences of repeated failure or lack of satisfaction with respect to the mastery of motor skills, with respect to perceptual and conceptual thinking, with respect to gaining parental and social acceptance, with respect to learning to think and communicate by means of symbols. The personality reacts in a most predictable and consistent way, with anxiety and depression, with negativism and aggression, with feelings of inadequacy and rejection, and with retreat to a less mature level, where failures are more tolerable. Anxiety, pervasive and poorly organized, has been ascribed by Bender [1] to the inability of the developing individual to gain satisfaction from his poorly integrated motor functions and self-concept. There is nothing in the present study to support or negate her thesis, but it is equally plausible that the anxiety, which is almost universal, results from continuing failure and parental disapproval. Certainly the negative parental attitudes that these children evoke can only augment their feelings of frustration and failure. These children, who need added maternal support to supplement their own motor and perceptual and social inadequacies, inevitably experience added anxiety when the support is not forthcoming. An explanation for the negative parental feelings is obvious. The child's need for support and protection is excessive and the parents' efforts in his behalf are correspondingly great, but these efforts are not rewarded by any concomitant progress in the child's acquisition of skills or of independence. A parent finds himself called upon to make an unusually large investment of effort and emotional response in behalf of a child whose limitations are apparently inexplicable and whose progress is unrewarding. Such a parent continues tirelessly in his efforts to improve the youngster's functioning and to seek medical and psychiatric explanations for the failures and inadequacies, but parental tolerance and sympathy do not maintain the same pace.

The net results of the neurological and psychological handicap can be measured most objectively by the two criteria of success in childhood, social adjustment and school progress. Without the motor skills and facility of communication of his peers, without the internal control of impulsivity that can enable him to conform to a group, without the self-assurance that comes from easy acquisition of expected skills, the child is socially inept and unacceptable. He can choose among the unsatisfactory alternatives of retaliatory aggression against the rejecting peers, or peaceable association with uncritical younger children, or solitariness. In the age of television, solitude is presently the most rewarding alternative. School progress, as has been demonstrated, is inescapably unsatisfactory. Language and perceptual limitations, distractibility, impulsivity, anxiety, and social ineptness augment one another in leading to failure. The teacher, confronted by a child of allegedly normal intelligence and minimal achievement, has been taught to look for an emotional disturbance as the explanation for failure, and so she interprets the problem as one of "laziness" or day-dreaming or emotional blocking, thereby obscuring the problem still further and compounding the child's feelings of inadequacy and anxiety.

The experience of this clinic would be worth very little if it merely added a few more cases and a bit more of quantitative data to the growing literature on the subject

of organic behavior disorder. However, the results of treatment of these cases give a basis for constructive handling of the problem. The first requisite is early recognition of the brain-injured child with early definition of both the weaknesses and strengths of his neurological and psychological apparatus. An interpretation should be given to the parents of the nature of the disability and the areas in which added help and protection are needed. Parents may require the support and encouragement of a knowledgable clinician in order to render, in turn, the added support and protection the child requires. Furthermore, parents need help in scaling their expectation to conform with the child's potentialities, help in learning to substitute their own external control for the child's lack of inner control, help in structuring and simplifying his environment so that he will not be tormented by his impulsivity and distractibility, and help in learning to communicate their acceptance of him in such a way as to provide him with a feeling of dignity and self-acceptance. In addition to enlightened parental support, the child may be benefited by the special clinical services of a speech therapist (where there is delayed or impaired speech) or a reading clinician (where there is a reading disability) or an occupational therapist (where incoordination is severe) or a psychiatrist (where anxiety is extreme). Pedagogical concepts need to be broadened so that these children receive the special attention they need, just as retarded and palsied and cardiac children and deaf children are now receiving educational recognition. Experience has shown that brain-damaged children thrive best academically in a simplfied environment where they cannot be distracted unduly by too many children or overly stimulated by an elaborately decorated classroom. Teaching techniques must compensate for visual or auditory or kinesthetic perceptual difficulties by using alternative sensory avenues where one avenue is primarily impaired. Opportunities for success must be provided within the academic setting to compensate for specific failures in the 3 R's. Finally, a vocational orientation consonant with existing abilities must be sought for and found in early adolescence. A note of optimism can be truthfully offered to parents, children, and teachers, namely, that the maturing organism has potentialities for compensation and development that are often surprising and unsuspected and that with conscientious effort and constructive assistance the outlook is rather better than the initial assessment would indicate.

SUMMARY AND CONCLUSIONS

Twenty-two cases of brain-injured children are studied and analyzed.

The distinctive clinical features are motor incoordination, perceptual difficulties, anxiety, social ineptness, speech and reading disabilities, and school failure.

An interpretation of the clinical syndrome is offered in terms of the dynamic effects of the brain damage.

Recommendations are made for clinical management, parental guidance, and pedagogical handling.

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Newborn Infants with Congenital Malformations or Birth Injuries

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Several of the major problems in special programs for handicapped children are the needs to devise effective methods of early case finding, of early referring for treatment and rehabilitation of high caliber, and of ongoing supervision for the necessary period of time. It has been suggested that the inclusion of specific items on the live birth certificates regarding the presence of a congenital malformation or a birth injury constitutes one method of approach to these major problems. Most of the states and some large cities have had such items on the live birth certificates for a number of years. Material from New York City will be presented to attempt to answer several questions about the use of such data:

1. What are some of the facts concerning the group reported on live birth certificates in New York City in 1953 and how do they compare with a similar group studied in 1951?[1]

2. What is current practice throughout the country with respect to the use of the information reported on congenital malformations or birth injuries?

3. Is follow-up of such reported infants an effective and productive tool in special programs for handicapped children?

Received for publication Sept. 20, 1955.

From the Bureau for Handicapped Children and Bureau of Records and Statistics, New York City Department of Health.

ANALYSIS OF THE GROUP STUDIED

Incidence

In 1953, in New York City, there were reported on live birth certificates 1438 newborn infants with a congenital malformation and 305 newborn infants with a birth injury, with over-all incidences of 8.90 and 1.89 per 1000 live births, respectively. In addition, in 1953, there were 74 newborn infants reported with symptoms referable to the respiratory process (dyspnea, cyanosis, asphyxia, difficulty in resuscitation, delayed respiration, etc.) and 109 newborn infants for whom the birth certificate questions regarding congenital malformation or birth injury were stated to be "questionable." These last two groups of 74 and 109 infants are not included in this study. These groups were also eliminated from the 1951 data.

The most frequent malformations reported were those of the extremities, central nervous system, genitourinary system, cleft palate and/or lip, and skin. Club foot, dactylism, cleft palate and/or lip, and hypospadias constitute the more frequent types of individual malformations.

The most frequent birth injuries reported were paralysis (primarily facial) and fractures.

A comparison of the 1953 and 1951 series in New York City reveals close similarity in the congenital malformation groups. On the other hand, the incidence of birth injuries in 1953 is lower, with the reported decrease occurring in all types except fractures (Tables 1, 2, and 3).

Incidence by Place and Type of Service at Birth.—The incidence of reported congenital malformations in the nonwhite is somewhat higher than that for the white (11.0 as com-

TABLE 1.—*Congenital Malformations by System: Incidence and Neonatal Mortality*

System	1953 Malformations Reported, No.	1953 Incidence per 1,000 Live Births	1953 Neonatal Deaths	1953 Neonatal Mortality, %	1951 Malformations Reported, No.	1951 Incidence per 1,000 Live Births	1951 Neonatal Deaths	1951 Neonatal Mortality, %
Extremities	612	3.79	31	5.1	660	4.06	44	6.7
Central nervous system	194	1.20	67	34.5	227*	1.39*	84†	37.0†
Genitourinary	158	0.95	10	6.5	152	0.93	8	5.3
Cleft palate and/or harelip	135	0.84	15	11.1	128	0.79	15	11.7
Skin	120	0.74	0	....	87	0.53	3	3.4
Gastrointestinal tract	70	0.43	20	28.6	79	0.49	18	22.8
Eye, ear, and nose	21	0.13	1	4.8	43	0.26	5	11.6
Heart	29	0.18	11	37.9	34	0.21	13	38.2
Miscellaneous	104	0.64	18	17.3	91	0.56	28	30.8
Total	1,438	8.90	173	12.0	1,501*	9.22*	218†	14.5†

* Anencephaly was not tabulated in the 1953 data. The 1951 data include 34 cases. The rate for central nervous system excluding these cases is 1.18. The over-all rate excluding these cases is 9.01.

† Excluding the anencephaly cases and deaths (all died in the neonatal period) the mortality per cent for central nervous system is 25.9. The over-all mortality per cent excluding these cases and deaths is 12.5.

TABLE 2.—*Congenital Malformations, more Frequent Types of Deformity, Incidence*

	1953 No.	1953 Incidence per 1,000 Live Births	1951 No.	1951 Incidence per 1,000 Live Births
Club foot	334	2.07	351	2.16
Adactylism, polydactylism, or syndactylism	194	1.20	205	1.26
Cleft palate and/or cleft lip	135	0.84	128	0.79
Cleft lip, alone	45	0.28	53	0.32
Cleft palate, alone	32	0.20	34	0.21
Cleft palate and cleft lip, alone	44	0.27	27	0.17
Cleft palate with other anomalies	14	0.09	14	0.09
Hypospadias	99	0.61	100	0.61
Spina bifida	43	0.27	73	0.45
Mongolism	47	0.29	46	0.28
Hydrocephalus	47	0.29	36	0.22
Anencephaly	*	*	34	0.21
Congenital heart disease	29	0.18	32	0.20
Erythroblastosis	29	0.18	30	0.18
Meningocele and encephalocele	39	0.24	29	0.18
Hemangioma and nevus	46	0.28	30	0.18
Imperforate anus	13	0.08	16	0.10

* Not included in 1953 study.

TABLE 3.—*Birth Injuries by Type and Site: Incidence and Neonatal Mortality*

Type	1953 Birth Injuries Reported, No.	1953 Incidence per 1,000 Live Births	1953 Neonatal Deaths	1953 Neonatal Mortality, %	1951 Birth Injuries Reported, No.	1951 Incidence per 1,000 Live Births	1951 Neonatal Deaths	1951 Neonatal Mortality, %
Paralysis	79	0.49	2	2.5	104	0.64	5	7.7
Facial	46	0.29			74	0.45		
Erb's	18	0.11			16	0.10		
Brachial	11	0.07			9	0.06		
Miscellaneous	4	0.02			5	0.03		
Fracture	67	0.41	5	7.5	61	0.37	1	1.6
Clavicle	26	0.16			31	0.19		
Lower extremities	12	0.07			14	0.09		
Humerus	18	0.11			12	0.07		
Upper extremities	9	0.06			4	0.02		
Other	2	0.01			0	....		
Intracranial injury or hemorrhage	19	0.12	8	42.1	24	0.15	10	41.7
Miscellaneous*	140	0.87	5	3.6	188	1.16	7	3.7
Total	305	1.89	20	6.6	377	2.32	26	6.9

* Includes contusions, abrasions, bruises, hematomas, lacerations, etc.

pared with 8.5 per 1000 live births). The over-all incidence of reported congenital malformations in municipal hospitals (10.5), in proprietary hospitals (10.0), and in ward patients in voluntary hospitals (10.6) is higher than that among private patients delivered in voluntary hospitals (7.3) (Table 4).

The incidence of reported birth injuries in the nonwhite and in the white is the same (1.9 per 1000 live births). The over-all incidence of reported birth injuries in municipal hospitals (2.1), in proprietary hospitals (2.3), and in ward patients in voluntary hospitals (2.5) is higher than among private patients delivered in voluntary hospitals (1.4) (Table 4).

The lower incidence of both the reported congenital malformations and the birth injuries in the private patient group delivered in voluntary hospitals in 1953 is a fact not found in the 1951 data. Whether this is a true difference or a factor of reporting alone is unknown, and this cannot be determined until several more years' data are studied.

Incidence by Birth Weight Group.—The incidence of reported congenital malformations in the group weighing less than 2500 gm. is more than twice that of the full-term group. This difference between the full-term and premature groups is the same as was observed in the 1951 data.

Because of the small numbers, it is not possible to see any trend in the birth weight distribution of the reported congenital malformations by system. However, in general, the systemic distribution seems to follow the total congenital malformation distribution by birth weight (Table 5).

The incidence of reported birth injuries in the full-term and premature groups is approximately the same—a finding similar to the 1951 data. As would be expected, the incidence of reported birth injuries is higher in the "4501 to 5000" and "over 5000" gm. weight groups, although the numbers are small (Table 5). Practically all of the babies with birth injuries in these two higher weight groups had fractures or paralysis.

TABLE 4.—*Incidence of Congenital Malformations and Birth Injuries by Place and Type of Service at Birth**

Place and Type of Service	1953 Live Births	Congenital Malformations		Birth Injuries	
		No.	Incidence/1,000 Live Births	No.	Incidence/1,000 Live Births
Hospital deliveries	159,290	1,423	8.9 (9.2)	302	1.9 (2.8)
A. Private patients	105,160	861	8.2 (9.5)	178	1.7 (2.8)
Voluntary	69,891	511	7.3 (9.6)	97	1.4 (1.9)
Proprietary	35,269	353	10.0 (10.7)	81	2.3 (3.0)
B. General service patients	54,070	559	10.3 (8.6)	124	2.3 (2.4)
Voluntary	24,056	254	10.6 (10.1)	60	2.5 (2.2)
Municipal	26,699	281	10.5 (7.7)	57	2.1 (2.7)
Federal	3,303	24	7.3 (4.5)	7	2.1 (1.2)
State	12	0	... (...)	0	... (...)
Nonhospital deliveries	2,279	15	6.6 (8.5)	3	1.3 (3.0)
Totals	161,499	1,438	8.9 (9.2)	305	1.9 (2.8)

* Corresponding rates for 1951 are indicated in parentheses.

TABLE 5.—*Congenital Malformations and Birth Injuries; Incidence and Neonatal Mortality, by Birth Weight*

Birth Weight, Gm.	1953 Live Births	Congenital Malformations					Birth Injuries				
		Incidence		Incidence per 1,000 Live Births	Neonatal Deaths	Neonatal Mortality, %	Incidence		Incidence per 1,000 Live Births	Neonatal Deaths	Neonatal Mortality, %
		No.	%				No.	%			
1,000 & under	903	6	0.4	6.6	4	66.7	2	0.6	2.2	2	100.0
1,001-1,500	1,065	25	1.7	23.5	15	60.0	11	3.6	10.3	6	54.5
1,501-2,000	2,497	70	4.9	28.0	24	34.3	3	1.0	1.2	1	33.3
2,001-2,500	9,777	150	10.4	15.3	23	15.3	7	2.3	0.7	1	14.3
2,501-3,000	37,069	359	25.0	9.7	38	10.6	56	18.4	1.5	1	1.8
3,001-3,500	64,489	481	33.4	7.5	40	8.3	84	27.5	1.3	3	3.6
3,501-4,000	35,797	265	18.4	7.4	16	6.0	89	29.2	2.5	4	4.5
4,001-4,500	8,058	50	3.5	6.2	4	8.0	29	9.5	3.6	1	3.4
4,501-5,000	1,242	11	0.8	8.9	1	9.1	14	4.6	11.3	0	...
Over 5,000	85	0	...	...	0	...	3	1.0	35.3	0	...
Not stated	927	21	1.5	22.8	8	38.1	7	2.3	13.3	1	14.3
Totals	161,499	1,438	100.0	8.9	173	12.0	305	100.0	1.9	30	6.6
		1,166		7.9	99	8.5	275		1.9	9	3.3

MORTALITY

This section on mortality presents data on the number of babies who had died by the time the public health nurse made the home visit or learned of the baby's death through weekly district infant mortality lists. Since the average home visit was made 36 days after birth, the data represent mortality for a period extending nine days beyond the conventional neonatal period (under 28 days). Since the neonatal period was the length of time used for mortality determination in the 1951 study, the two sets of data are not entirely comparable; however, any difference should be weighted in favor of the 1951 study.

Mortality data in a program for handicapped children, of course, represent only a crude but final end-result. Theoretically at least, an effective program for handicapped children should be able to reduce mortality as well as to prevent permanent disability to a great extent. Deaths attributed to congenital malformations and birth injuries at present comprise 30% of all neonatal mortality in New York City.

Tables 1 and 3 present the data on mortality of infants with congenital malformations or birth injuries. The over-all mortality for infants reported with congenital malformations is 12.0%, which is comparable to that of the 1951 study (12.5%). All types of congenital malformations in 1953 show a lower mortality than in 1951, except for those of the genitourinary and gastrointestinal systems (which are higher) and cleft palate and cardiovascular system (which are the same). The over-all mortality for infants reported with birth injury is 6.6%, which is approximately the same as that of the 1951 study (6.9%). The 1953 series shows a higher mortality among babies reported with fractures and a lower mortality among babies reported with paralysis. Other types of birth injury show the same mortality in the two series.

Analysis of the mortality by birth weight distribution reveals an over-all mortality of 12.0% for the total group of infants reported with congenital malformations. The

mortality among the full-term group is 8.5%, as compared with that of 26.3% among the group prematurely born. The birth weight groups in the 1953 data show a lower mortality, as compared with the 1951 series, except in the "1001 to 1500" gm. group (where the mortality is almost the same) and in the "3001-3500" and "3501-4000" gm. weight groups (where the mortality is higher in the 1953 series) (Table 5).

The 1953 birth injury group shows an over-all mortality of 6.6%. The mortality in the full-term group is 3.3%, and in the prematurely born group it is 43.5% (Table 5). Because of the small numbers in the various birth weight groups, it is not possible to make any detailed comparisons with the 1951 data.

CURRENT PRACTICE THROUGHOUT THE UNITED STATES

Because of the progress made in the last several decades in the saving of infant lives after the first month of life, great interest has now been centered upon the perinatal period. Public health administrators and clinicians in maternal and child health and crippled children's programs have tended to use both the fetal death and live birth certificates to study some aspects of the remaining perinatal problem, in regard to both mortality and, to a less extent, morbidity. As a corollary, some state and local health departments have included questions on the live birth certificates pertaining to the incidence of congenital malformations and birth injuries. While it is recognized that the data secured from the inclusion of these new items on the live birth certificates must necessarily represent incomplete information, nevertheless it has been postulated that such inclusion is justified from three points of view: 1. It gives a minimum estimate of the extent of the problem. 2. It represents a source of early case finding. 3. It provides an easy mechanism for instituting follow-up and referral for care.

In spite of the fact that many state and local communities now include questions regarding congenital malformations and birth injuries on the live birth certificates, there have been few reports in the literature describing the use and value of such data. For this reason, this section of the report will present (1) the results of a questionnaire survey of current practice in the states and territories of the United States and in large urban areas and (2) the results of public health nursing follow-up of babies reported on live birth certificates in 1953 in New York City to have a congenital malformation or birth injury.

In the spring of 1953, questionnaires concerning current policies for follow-up of babies reported via live birth certificates to have a congenital malformation or a birth injury were sent to the directors of maternal and child health programs and of crippled children's services in the states and territories and in the 10 largest cities in the United States. Table 6 presents a summary

TABLE 6.—*Type of Follow-Up in United States in 1953*

Type of Public Health Nursing Follow-Up*	States, Territories, & Cities, No.
1. Routine on all CM or BI	12
Routine home visiting on all by PHN	9
Letter sent to all parents	1
Possibly routine home visiting on all by PHN	2
2. Partial on some CM or BI	21
Routine home visiting by PHN in organized health areas	1
Not routine, but some followed by PHN	3
PHN visits on all reporting treatment needs to CC Program	1
PHN visits on CM or BI acceptable to CC program	1
Private physician contacted first; if permission is given, PHN visits private cases	0
Letter sent to private physician describing CC services available	1
PHN visits or letter sent to private physician	1
PHN visits on all ward-born	1
Congenital malformations only	4
PHN visits those acceptable to CC program	1
PHN contacts pricate physician for permission	1
PHN visits those not under private care.	1
PHN visits all CM	1
Cleft palate only—private physician called; if no plan, PHN visits	1
Letter sent to private physician; if reply not satisfactory, referred to County Welfare Director	1
3. No follow-up	14
4. Items not on birth certificates	6
5. No reply	9
Total	62

* CM, congenital malformations; BI, birth injuries; PHN, public health nurses; CC, crippled children.

of the data received in the replies to the questionnaire. Nine states and territories and three cities do some type of routine follow-up. In 20 states and territories and 1 city partial follow-up is done on a selected basis, usually economic, diagnostic, or whether the patient is under care of a private physician. In 13 states and territories and 1 city there is no type of follow-up, and in 6 states and territories the items are not provided on the live-birth certificates.

The type of follow-up reported on the questionnaire usually consists of home visiting by a public health nurse. Less frequently, it may consist of contact to the family or physician by letter or telephone with subsequent home visiting by the public health nurse, if the private physician requests or consents to the service or if some particular service is known to be needed.

Of the replies received from the states, territories, or cities, one * from Erie County, N. Y., indicated that a study of the results of follow-up had been made in 1952. This study showed that most of the infants were over 2 to 3 weeks of age by the time the referral for home visiting was in the hands of the public health nurse and that congenital malformations are under-reported on the birth certificates. It was concluded that the follow-up of physical defects at birth was not a particularly effective tool for improving care to handicapped children in that community.

STUDY OF FOLLOW-UP OF NEWBORN INFANTS REPORTED IN NEW YORK CITY

Method of Study

On Jan. 1, 1953, the Bureau for Handicapped Children, the Bureau of Public Health Nursing, and the Bureau of Records and Statistics of the New York City Department of Health instituted a revised plan of public health nursing home visiting to include all babies reported on the 1953 live-birth certificates to have a congenital malformation or birth injury. This plan consisted of at least one visit to the home of all reported babies by a public health nurse, with subsequent visits by the nurse on the basis of individual needs. The home visiting was shared by public health nurses on the staff of the City Health Department and of the three voluntary public health nursing agencies in the City. A study form was used which was filled out by the public health nurse at the time of the first home visit and then sent to the Bureau of Handicapped Children for medical and statistical analysis.

Results of Home Visiting

Age of Infants at Time of First Home Visit.—Where data were available (1425 cases), the average age of the infant at the time of the first visit to the home by the public health nurse was 36 days. This age represents a time well beyond the period of hospital discharge for most newborn infants in New York City, since the usual age of discharge is five to seven days. For this group, which is more heavily weighted with prematures and infants requiring more extensive care than the over-all live birth group, the hospital discharge date is probably later.

Type of Medical Care. — Birth Injury Group: Of the 305 babies with a reported birth injury, by the time the first home visit was made by the public health nurse, 235 infants (77.0%) were alive and under some type of medical care; 20 infants (6.6%) had died; 26 infants (8.5%) were definitely known not to be under medical care. There was no information on 24 infants (7.9%), usually because the family could not be located. Of the 235 infants under medical car, most of them (152, or 65%) were under the care of a private physician alone; half under the care of a private physician were under the care of a general practitioner and one-sixth were under care of a qualified pediatrician.† Hospital outpatient depart-

* Moser, W. E.: Personal communication to the authors, June 25, 1954.

† A qualified pediatrician is defined as a physician who is certified by the American Board of Pediatrics or who has the rank of associate attending or higher on the staff of a hospital approved by the Council of Medical Education and Hospitals of the American Medical Association for residency training in pediatrics.

ments alone were caring for 54 infants (23%) of the total 235 infants under care. Of the hospital outpatient services caring for the infants, 60% of the infants were under the care of hospitals approved by the Bureau for Handicapped Children ‡ for reimbursement under the Medical Rehabilitation Program and 40% were under the care of hospitals not so approved. There were only 14 infants (6.0% of those under care) who were under the care of a Department of Health or private agency child health station alone for health supervision, and 5 other infants were under care of a child health station and some other agency, usually a hospital. Only 7 of the 235 infants under care were on the inpatient service of a hospital, and only 2 were under the care of a hospital approved by the Bureau for Handicapped Children (Table 7).

Congenital Malformation Group: Of the 1438 babies with a reported congenital malformation, by the time the first home visit was made by the public health nurse, 1056 infants (73.5%) were alive and under some type of medical care; 173 infants (12.0%) had died; 98 infants (6.8%) were definitely known not to be under medical care. Data were not available on 111 infants (7.7%); this group includes those not located and a few for whom the data were not recorded. Of the 1056 infants under medical care, 592 (56%) were under the care of a private physician alone; almost half under the care of a private physician were under the care of a general practitioner, one-fifth were under the care of a qualified pediatrician, and 8% were under the care of a qualified orthopedist. Hospital outpatient departments were caring for 225 infants (21% of the total 1056 infants under medical care). Of the hospital outpatient services caring for the infants, 63% of the infants were under the care of hospitals approved by the Bureau for Handicapped Children for reimbursement under the medical Rehabilitation Program

TABLE 7.—*Type of Medical Care*

Type of Medical Care	Birth Injuries*	Congenital Malformations*
Private physician (only)	152 (49.8)	592 (41.2)
General practitioner	74	259
Qualified specialist	40	214
Other physician	14	55
Not listed	24	59
Health insurance plan	..	5
Hospital service (only)	59 (19.4)	290 (20.8)
Outpatient service	54	225
Inpatient service	5	74
Health department or private well-child clinic (only)	14 (4.6)	53 (3.7)
Private physician and hospital service	5 (1.6)	82 (5.7)
General practitioner and OPD	2	17
Qualified specialist and OPD	1	15
Other physician and OPD	..	6
Not listed and OPD	..	3
General practitioner and IPD	1	16
Qualified specialist and IPD	1	18
Other physician and IPD	..	7
Health department or private well-child clinic and OPD	5 (1.6)	22 (1.5)
Health department well-child clinic and general practitioner	.....	3 (0.2)
Private sanitarium	.....	5 (0.4)
Died	20 (6.6)	173 (12.0)
Not under care	26 (8.5)	98 (6.8)
No contact	24 (7.9)	111 (7.7)
Total	305 (100.0)	1,438 (100.0)

* Percentages are given in parentheses.

‡ An approved hospital is defined as a hospital which reasonably meets the standards established by the Bureau for Handicapped Children and is recommended for approval by the respective Advisory Committee to the New York City Commissioner of Health for participation in the Medical Rehabilitation Program.

and 37% were not. There were 53 infants (5.0% of those under care) who were under the care of a Department of Health or private agency child health station alone; and 25 other infants were under the care of a child health station and some other agency. Of the 1056 under care, 115 infants (10.9%) were on the inpatient service of a hospital, of which half were under the care of a hospital approved by the Bureau for Handicapped Children (Table 7).

Status of Infants.—Of the 1438 infants reported with a congenital malformation at birth, 909 (63.2%) were found at first home visit to have malformation still present. An additional 106 (7.4%) infants had previously had the malformation but it had been removed or corrected by the time of the home visit; most of this group had a malformation of the extremities, usually polydactylism. No malformation was found in 139 infants (9.7%); 173 (12.0%) had died, and the condition of 111 infants (7.7%) was not known.

In the birth injury group, 125 infants (41.0%) had the condition present, and 1 additional infant with a birth injury (a fracture) had had it corrected. One hundred thirty-seven infants (44.9%) had no evidence of a birth injury at the time of home visit; most of this group had had reported on the live birth certificates minor injuries such as contusions, abrasions, bruises, lacerations, etc., which had healed by the time of the home visit. Twenty infants (6.6%) had died, and the status of twenty-two infants (7.2%) was unknown (Table 8).

In the congenital malformation group, of the 909 babies with the malformation present at the time of home visit all but 6.7% were under medical care. Of the 106 babies whose malformation had been corrected, all but 38.7% were under medical care. Of the 139 infants in whom evidence of a malformation was not found, all but 11.5% were under medical care.

TABLE 8.—*Status of Baby at First Home Visit, Status of Medical Care, and Plans for Future Medical Care*

	Total	Condition Present	Condition Previously Corrected	Condition Not Present
Congenital malformations				
Under medical care	1,036	848	65	123
Not under medical care	118	61	41	16
Plans made	42	26	12	4
No plans made	63	35	20	8
Unknown	13	..	9	4
Total	1,154*	909	106	139
Birth injuries				
Under medical care	231	119	1	111
Not under medical care	32	6	..	26
Plans made	10	5	..	5
No plans made	16	1	..	15
Unknown	6	..	..	6
Total	263†	125	1	137

* Does not include 173 deaths and 111 no contacts.
† Does not include 20 deaths and 22 no contacts.

In the birth injury group, practically all (95.2%) of those having a birth injury were under medical care and all but 19.0% of those infants in whom no evidence of an injury was found were under medical care (Table 8).

The private patient group had a higher percentage of patients under medical care (97%) than the ward group (81%). The white group had a higher percentage (94%) than the nonwhite group (75%).

If Child Was Not Under Medical Care, Had Family Already Made Plans for Medical Care? Congenital malformation group. Of the 909 infants who were found at home visit to still have a malformation present,

848 (93.3%) were already under medical care; 26 (2.9%) were not under medical care but the family had made plans for such care, and 35 infants (3.8%) were not under medical care and no plans for such care had been made.

Two hundred forty-five infants were found to no longer have a congenital malformation present at the time of the first home visit. Of this number, 188 (76.8%) were already under medical care; 16 (6.5%) were not under medical care but their family had made plans for such care; 28 (11.4%) were not under medical care and no plans for such care had been made, and the status of 13 infants (5.3%) was unknown (Table 8).

As might be anticipated, the private group had a higher percentage under care than the ward group, and the white group had a higher percentage under care than the nonwhite.

Birth injury group. Of the 125 infants who were found at home visit to still have an injury present, all but 6 were under medical care; 5 infants (4.0%) had already had a plan for medical care made by the family, and 1 infant (0.8%) had no such plan made.

One hundred thirty-eight infants were found to no longer have a birth injury present at the time of the first home visit. Of this number, 112 (81.2%) were already under medical care; 5 (3.6%) were not under medical care but their family had made plans for such care; 15 infants (10.9%) were not under medical care and no plans for such care had been made, and the status of 6 infants (4.3%) was unknown (Table 8).

The private group had a higher percentage of infants already under medical care than the ward group, and the white group had a higher percentage under care than the nonwhite.

If Family Had Not Made Plans for Medical Care, Was the Public Health Nurse Able to Help? Congenital malformation group. Of the 909 infants found to still have a malformation present at the first home visit, plans for medical care had been made by the family for all but 35 infants (3.8%). Of this group of 35 infants, the public health nurse was able to assist the family in planning for and referral to medical care for 28 infants (80%) and the families of 7 infants (20%) did not accept assistance (3.1% and 0.7%, respectively, of the 909 infants).

Of the 245 infants found not to have a malformation present at the first home visit, for all but 41 (16.7%) plans had been made by the family for medical care. Of this group of 41 infants, the public health nurse was able to assist the family in planning for and referral to medical care for 13 infants (32%). The families of 15 infants did not accept assistance (36%); information on medical care of 13 infants (32%) could not be secured (5.3%, 6.1%, and 5.3%, respectively, of the 245 infants) (Table 9).

TABLE 9.—*If Family Had Made No Plans, Was Nurse Able to Help?*

	Cases, No.		
	Total with No Plans	Nurse Able to Help	
		Yes	No
Congenital malformations	63	41	22
Birth injuries	16	9	7
Total	79	50	29

The public health nurse was able to assist the family in planning for medical care and in making referral for 10% of the nonwhite infants, 8% of the ward infants, 2% of the white infants, and none of the private infants.

Birth injury group. Of the 125 infants found to still have a birth injury present at the first home visit, the family had made plans for medical care for all but 1 infant. The public health nurse was able to assist the family in planning and referral for medical care of this one infant.

Of the 138 infants found not to have a birth injury present at the first home visit, for all but 21 infants (17.4%) the family had made plans for medical care. Of this group of 21 infants, the public health nurse was able to assist the family in planning and referral for medical care of 8 infants (38%), and the families of 7 infants (33%) did not accept assistance; for 6 infants (29%) information regarding medical care

could not be secured (5.8%, 5.1%, and 4.3%, respectively, of the 138 infants) (Table 9).

The public health nurse was able to assist the families of 7% of the infants born on ward service, 6% of the nonwhite infants, 3% of the white infants, and 1% of the private infants.

Status of Family and Home Situation.—In the cases of the 1154 infants reported with a congenital malformation who were alive and contacted, 77 (6.7%) families were found to have an additional family, social, or health problem (finances, other illness, housing, emotional disturbance, social difficulty, etc.). The percentages of families with "other problems" were 19% and 5% for the nonwhite and white groups, respectively, and 17% and 3% for the ward and private groups, respectively (Table 10).

Of the 263 infants reported with a birth injury who were alive and contacted, 18 (6.8%) families were found to have an additional family, social, or health problem. The percentages of families with "other problems" were 15% and 5% for the nonwhite and white groups, respectively, and 16% and 1% for the ward and private groups, respectively (Table 10).

Did the Public Health Nurse Plan to Continue to Work Further with the Family? Of the 909 infants in whom a congenital malformation was still present, the public health nurse was planning to continue follow-up by home visiting with 234 families (27.9%) and to work further via the child health stations with 23 additional families (2.5%). Of the 245 infants in whom a congenital malformation was no longer present, the public health nurse was planning to continue follow-up by home visiting with 31 families (12.7%) and to work further via the child health stations with 12 additional families (4.9%). The public health nurse planned to work further with a higher percentage of ward families (31%) than private families (16%) and with a higher percentage of nonwhite families (30%) than with white families (21%) (Table 11).

Of the 125 infants in whom a birth injury was still present, the public health nurse was planning to continue home visiting with 36 families (28.8%) and to work further via the child health stations with 11 additional families (8.8%). Of the 138 infants in whom a birth injury was no longer present, the public health nurse was planning to continue home visiting with 23 families (16.7%) and to work further via the child health stations with 4 additional families (2.9%). The public health nurse planned to work further with a higher percentage of ward families (38%) than with private families (9%) and with a higher percentage of nonwhite families (41%) than with white families (17%) (Table 11).

TABLE 10.—*Family and Home Situation*

	Cases, No.		
	Total	Congenital Malformations	Birth Injuries
Satisfactory	1,133	917	216
Not satisfactory	95	77	18
Unknown	189	160	29
Total	1,417	1,154*	263†

* Does not include 173 deaths and 111 no contacts.
† Does not include 20 deaths and 22 no contacts.

TABLE 11.—*Did Nurse Plan to Continue to Work Further with Family?*

	Cases, No.		
	Total	Congenital Malformation	Birth Injuries
No	888	720	168
Yes	394	320	74
Home visiting	344	285	59
Through child health station	50	35	15
Unknown	135	114	21
Total	1,417	1,154*	263†

* Does not include 173 deaths and 111 no contacts.
† Does not include 20 deaths and 22 no contacts.

COMMENT

Pertinent facts concerning the infants reported are that (1) by and large the 1953 data on infants reported with congenital malformations or birth injuries in New York City closely parallel, with some exceptions, the 1951 data from New York City; (2) the 1953 reported birth injury incidence is lower than that in 1951; (3) there was no discernible monthly trend in the reporting

of congenital malformations at birth in 1953 in New York City; (4) there is a lower incidence of reported congenital malformations and birth injuries among private patients delivered in voluntary hospitals in New York City; (5) babies reported with congenital malformations in 1953 in New York City had approximately the same mortality as in 1951; (6) there was a lower incidence of reported congenital malformations in the white group. It is not known whether these data reflect true findings or whether they are merely phenomena relating to the accuracy of reporting. Nevertheless, some interpretation may be pertinent, although this type of analysis should be repeated in subsequent years.

It is possible that the lower incidence of reported birth injuries in the city may be due to an improving level of obstetric care. Certainly a previous study of 1948 data [2] in New York City substantiated the opinion that there were some important preventable obstetric factors in the birth injuries reported in that year.

The fact that there was no discernible monthly trend in the incidence of reported congenital malformations in New York City in 1953 merely means that, for that year, virus disease in pregnancy seemed not to play a significant epidemiological role in the causation of reported congenital malformations. Such studies should, however, be repeated annually.

The fact that babies reported with congenital malformations in 1953 had approximately the same mortality as in 1951 is indicative of the need for further research, since congenital malformations rank among the first three major causes of infant and neonatal mortality. In June, 1953, the Bureau for Handicapped Children of the City Health Department expanded its list of diagnostic conditions eligible for payment for inpatient hospital and rehabilitation care to include many types of congenital malformations previously not covered by the program. It would be interesting and important to determine how many of the 1438 infants reported with a congenital malformation received care through the Bureau for Handicapped Children payment program. It is essential to know whether any of the deaths in infants with congenital malformations had preventable factors; such a study is now under way. Studies such as these are important in planning and administering medical care programs for handicapped children.

The foregoing data concerning the results of home visiting may be summarized as follows: 1. The average age of the infants at the time of the public health nurses' first home visit was 36 days. 2. At the time the public health nurse visited the home, most of the infants were under medical care. 3. Sixty-three per cent of the infants with congenital malformations reported at birth and forty-one per cent of the infants with birth injuries reported at birth still had the condition present by the time of the public health nurses' first home visit. 4. The private and white groups had the highest percentages of infants under medical care. 5. The ward and nonwhite groups had the highest percentages of infants for whom no plan for medical care had been made. 6. The public health nurse was able to help about two-thirds of the families whose infants were not under medical care to make a plan for medical care; the ward and nonwhite groups were more in need of such help. 7. Seven per cent of the families of the congenital malformation group and of the families of the birth injury group, excluding deaths and no contacts, had an additional family, social, or health problem; the percentages were higher in the nonwhite and ward groups than in the private and white groups. 8. The public health nurse decided to work further with about one-fourth of the families; the percentages were higher in the nonwhite and ward groups than in the private and white groups.

It would appear from the above summary of facts that, for New York City, at least at the present time, a revision of the policy of public health nursing home visiting in the congenital malformation and birth injury groups is indicated. Instead of visiting all

the babies in both groups, as was done in 1953, it would be sounder to limit the visiting to the ward category, since the ward category had the lowest percentage of babies under medical care, the highest percentage of babies for whom no plan for care had been made, the highest percentage whom the public health nurse was able to assist in making a plan for medical care, and the highest percentage of other family, social, or health problems.

The fact that such a high percentage of infants in New York City was under medical care at the age of 36 days of life is very gratifying. However, when the pattern of medical care is analyzed more closely, the picture becomes one of greater concern. Most of the infants under the care of a private physician were not under the care of a qualified specialist in any of the indicated respective medical specialty fields—pediatrics, orthopedic surgery, physical medicine and rehabilitation, general surgery, etc.—and many of the infants under the care of outpatient or inpatient services of hospitals were not cared for by "approved" hospitals. Thus, while the picture is relatively good from a quantitative point of view, qualitatively there is considerable need for improvement. Since all of the congenital malformations and birth injuries reported were found within 48 hours after birth, it is possible that the plans for the medical care of the infants already under care were made while the infants were in the newborn nursery of hospitals with maternity and newborn services. The medical staff responsible for the care of the newborn nursery then becomes the key one in planning the ongoing medical care of the infants, and it is this medical staff which should be reached more effectively.

The fact that the infants as a group were on the average 36 days of age by the time of the public health nurse's first home visit would seem to indicate that in most instances the delay is too great. It is reasonable to assume that the public health nurse would be able to assist the family more effectively in many ways if the home visits were made earlier. This assistance applies to such aids as preparing for the homecoming of the infant; making sure that appropriate equipment, heat, space, etc., are provided for the infant; instructing the mother in the care of her baby; assisting the family in planning for adequate medical care, etc. Since about one-half of the 36-day period is consumed in just transmitting the newborn referral cards to the respective health districts for home visiting, there are two possible solutions to this problem—either speeding up the process of referral or having the referral come directly from the hospital newborn nursery service to the public health nurse in the community. The latter method has the added potential advantage of the hospital personnel's familiarity with the families and their problems, so that they would be able to make referrals more effectively and selectively for public health nursing. This latter method, however, has the disadvantage inherent in any plan which is dependent on staff where there is usually heavy turnover and where there is a large case load involved. Other methods of referral are now being tried.

It is interesting that 9 of the 48 states and territories and 3 of the 5 large cities answering the questionnaire have a policy of routine public health nursing follow-up of all infants reported via live birth certificates to have a congenital malformation or birth injury and that 20 of the 48 states and territories and 1 of the 5 large cities do some partial follow-up of the infants reported. As far as is known, only one of the communities reporting had studied its results. It is suggested that other communities where such babies are being followed also perform studies of their results. Results found in one community may not necessarily be applicable to any other community.

SUMMARY

This paper presents data from a study of follow-up of babies with a congenital malformation or birth injury reported on live birth certificates in New York City in 1953. The over-all incidence was 8.90

babies with congenital malformations and 1.89 babies with birth injuries per 1000 live births. While there are many similarities between the 1953 and 1951 studies in New York City, the 1953 data show a lower incidence of reported birth injury. There was no monthly trend discernible in the congenital malformations reported. There was a lower incidence of infants with reported congenital malformations and birth injuries among private patients delivered in voluntary hospitals in 1953.

The average age of the infants at the time of the public health nurse's first home visit was 36 days. By that time most of the infants were under medical care, although a high percentage was not under the care of qualified specialists or approved hospital services. The private and white groups had the highest percentage of infants under medical care. The public health nurse was able to assist one-half of the families whose babies were not under medical care to make a plan for care; the ward and nonwhite groups were more in need of such help. Seven per cent of the families of the congenital malformation groups and of the families of the birth injury group had an additional family, social, or health problem; the percentages were higher in the ward and nonwhite groups. The public health nurse planned to work further with one-fourth of the families; again, the percentages were higher in the ward and nonwhite groups.

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Children with Hernias, Testes, and Female External Genitalia

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Any doctor dealing with infants and children may encounter patients with inguinal hernias. We have seen three young patients with the external characteristics of females, each of whom had inguinal hernias. Subsequently, these children were proved to have testes within their inguinal canals and to have no internal female genitalia. Such cases present multiple problems in management.

There is adequate authority for recommending surgical repair of inguinal hernias early in infancy and childhood.* Only approximately 10% of such hernias occur in females. Although most authors state that an ovary and Fallopian tube may be found in the hernial sac of a female child, few of them state the incidence of this finding. Gross [1] does not mention it in the 10% of females in his series of more than 8000 cases of inguinal hernia in infants and children. Potts, Riker, and Lewis [2] recorded three sliding hernias of the ovary and tube in seven female infants under 18 months of age. Undoubtedly ovaries are encountered in hernia sacs fairly frequently but are not reported. However, the finding of testes with inguinal hernias in apparently normal female children must be rare. We know of no recorded series of such cases. Consequently, these three cases are reported as being of general interest but of real concern to the obstetrician, pediatrician, surgeon, and endocrinologist.

Submitted for publication Oct. 19, 1955.

* References 1 and 2.

REPORT OF CASES

CASE 1.—A 5-year-old child was first seen on Jan. 28, 1952. The presenting symptom was a tender swelling in the right inguinal region of three months' duration. The past history revealed that at birth the obstetrician suspected some type of genital abnormality because of enlarged and wrinkled labia. When this suspicion was imparted to the parents, they sought the advice of a pediatrician, who assured them that the child was a normal female. The child was raised as a girl and exhibited normal female characteristics.

Examination revealed an apparently normal 5-year-old girl. There was a swelling in the right inguinal region which was reducible. A 2 cm. mass barely palpable in this region was completely reducible. The external genitalia seemed to be those of a female even on close examination, although only a small opening was noted at the site of the vaginal orifice. A diagnosis of right indirect inguinal hernia containing ovary was made.

Surgery was performed on Feb. 6, 1952. A right indirect inguinal hernia was found. Attached to the medial wall of the hernia sac was a smooth, ovoid structure somewhat resembling a testis. The mass was removed because it was believed that the child was a female and that the mass probably represented a single accessory gonad, probably a testis. The hernia was repaired.

After surgery the external genitalia were closely inspected under anesthesia. The labia majora appeared somewhat enlarged and corrugated like scrotal skin. The labia minora and vaginal opening were normal. The clitoris was of average size or slightly enlarged. The vaginal canal was examined with an ear speculum. It was of average depth, but a cervix could not be seen. A photograph was made after surgery to show the child's general development and female-appearing external genitalia (Fig. 1).

Fig. 1 (Case 1).—A 5-year-old child after surgery for right inguinal hernia. Testis found in inguinal canal. Later found to have testis in left inguinal canal and to have no uterus, tubes, or ovaries.

Microscopic section of the mass removed with the hernia sac proved it to be an immature testis in which the spermatic tubules showed Sertoli cells and immature spermatogenic elements. In the loose interstitial tissue a few clusters of Leydig cells were present. In one of the sections a somewhat flattened, tubular structure, apparently an abortive vas deferens, was included. No epididymis was seen.

Subsequently this child was studied at the Los Angeles Children's Hospital. The gross findings were confirmed. The 24-hour urinary 17-ketosteroid excretion was 1.2 mg. X-rays of the wrist bones showed that the bone age was compatible with the chronological age. A laparotomy was performed. There was no evidence of intra-abdominal uterus, tubes, or ovaries. Another mass was found in the left inguinal canal. A biopsy was done and it proved to be an immature testis. This gonad was not removed.

The child is still being raised as a girl and is showing apparently normal female development.

Case 2.—On March 1, 1952, three weeks after the first child underwent surgery, the mother delivered another child, her third, who appeared to be a normal female (Fig. 2). However, because of the recent experience with the first child, the inguinal regions of the second child were closely examined and gonads were palpated in the upper portion of each labium. It was noted that the labia were slightly swollen and wrinkled. A slightly enlarged clitoris was present. A vaginal opening was seen (Fig. 3). The child was examined by several pediatricians, each of whom remarked that without foreknowledge and a very thorough examination the child would be considered a normal female.

This child was also studied at the Los Angeles Children's Hospital. The gross findings were confirmed. The 24-hour urinary excretion of 17-ketosteroids was 0.2 mg. A cystogram revealed a normal bladder. A combined vaginal cystourethro-

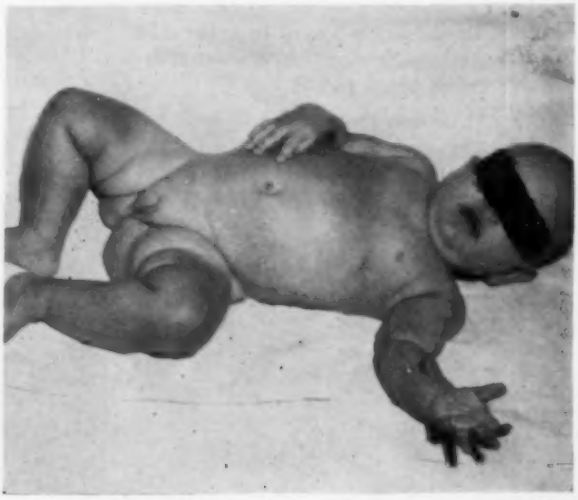

Fig. 2 (Case 2). — Sibling of child shown in Figure 1. Later found to have a testis in each inguinal canal and to have no uterus, tubes, or ovaries.

Fig. 3 (Case 2).—Close-up of external genitalia of child shown in Figure 2.

gram was attempted but could not be done, as the vagina could not be entered with a catheter. A laparotomy was performed. No intra-abdominal uterus, tubes, or ovaries were found. Structures resembling spermatic cords were seen descending and passing through the internal abdominal rings. Each scrotal-like labium contained a gonad with an associated tube, appearing grossly more like a testis and epididymis than an ovary. A biopsy was done and it was reported as immature testicular tissue. The gonads were not removed.

This child is being raised as a girl and is showing normal progress.

CASE 3.—This infant was born on Oct. 23, 1953, and was considered to be a normal female. No abnormalities were noted on the first examination or during the postpartum hospital stay. The child was seen at one month of age for routine examination. The mother had noted a swelling in the right inguinal region of three days' duration. This swelling was confirmed, and a less marked swelling was noted in the left inguinal region. In both swellings a small, hard mass suggestive of a gonad was palpated. Neither gonad was reducible. A diagnosis of bilateral indirect inguinal hernia, each containing a gonad, was made. Because of the previous experience with Case 1 and Case 2, it was considered that these gonads might be testes. The infant was carefully examined, but the external genitalia appeared definitely to be those of a female (Figs. 4 and 5).

Surgery was performed on Nov. 24, 1953. An incision was made in the skin fold overlying the right internal inguinal ring. The hernia sac was readily identified and opened and found to contain a gonad approximately 1.4 × 1.0 cm. It had an appearance compatible with that of a testis. It was attached to a cord-like structure containing a firm, fine tubular structure which felt like a vas deferens on palpation. Another incision was made over the

Fig. 4 (Case 3).—One-month-old infant with bilateral inguinal hernia, a testis in each inguinal canal, and no uterus, tubes, or ovaries.

Fig. 5 (Case 3).—Vaginal orifice and labia minora of child shown in Figure 4.

left internal inguinal ring. The findings on this side were identical with those on the left. Therefore, the incisions were joined across the midline and the peritoneal cavity was opened vertically in the midline. No female internal genitalia could be found by visualization or palpation. A biopsy of the gonad on the right was done. Biopsy of the left gonad was not done because it was identical in appearance with that on the right. The hernia sacs were individually closed at the neck and excised. The cord structures and gonads were preserved.

After the operation a large ear speculum was introduced into an essentially normal-appearing vagina. No cervix was seen.

A microscopic section of the tissue proved it to be from an immature testis, showing closely packed seminiferous tubules with no evidence of spermatogenesis, but containing spermatogonia and Sertoli cells. The tubular basement membranes appeared normal, and although the interstitial tissue was rather scanty, it contained normal Leydig cells. A portion of the tunica albuginea was present (Fig. 6).

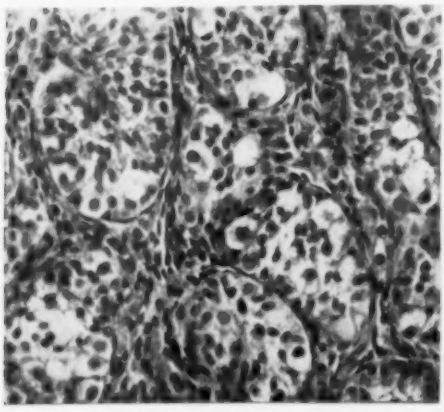

Fig. 6 (Case 3).—Photomicrograph of section of gonad from right inguinal region, showing immature testis. The biopsies performed in Case 1 and Case 2 showed similar microscopic findings; reduced approximately ⅓ from mag. × 250.

Additional studies were done to aid in the classification of this infant. X-rays of the wrist bones showed the bone age to be compatible with the chronological age. The 24-hour urinary excretion of 17-ketosteroid substances was 4.6 mg. on one occasion and 1.5 mg. on another. These increased values are not adequately explained. The results of a skin biopsy were reported as being consistent with those of a boy. At the time of the skin biopsy one was also done of the left gonad. The microscopic sections showed an immature testis, the findings being exactly the same as the microscopic findings of the biopsy of the right testicle at the original surgery.

The infant was studied at the University of California Medical Center and all of the findings and conclusions confirmed. She is developing as a normal girl.

COMMENT

Obviously these patients are difficult to classify. They seem to present very similar problems of intersexuality. By virtue of the fact that they have male gonads and female secondary sexual characteristics, they would ordinarily be classified as male pseudohermaphrodites.

These patients may eventually fall into a somewhat different classification. Several adults have been described who have feminine inclinations and physique, well-developed breasts, and a female distribution of hair, except that the axillary and pubic hair is sparse or absent.† The vaginal introitus, labia, and clitoris appear normal for adult females but are sometimes smaller than average. Most of the patients have inguinal hernias. The uterus, tubes, and ovaries are absent. The gonads are situated somewhere along the inguinal canal or are in the usual position for ovaries. The gonads are indistinguishable histologically from immature testes. The epididymis is absent or rudimentary. Such patients differ from the usual male pseudohermaphrodite in that the structures derived from both the Müllerian and the Wolffian ducts are rudimentary or absent. These persons reach adulthood as females. They have normal sexual attraction toward males. Many are married and have had satisfying intercourse but, of course, do not menstruate and are sterile.

In those patients in whom the gonads have been removed hot flashes have developed. Both of Novak's patients had severe menopausal symptoms after gonadectomy. It is striking to note the marked familial tendency. Schneider, Van Ommen, and Hoerr [3] emphasized this in particular. They operated upon two members of one family with this syn-

† References 3-8.

drome and believe that four other members of the family were similar intersexuals. Two of Novak's patients are siblings.

Novak [8] described the identical syndrome in two sisters, and, because of the histology of the gonads removed from each sister, he called the gonads testicular tubular adenomas. He described small areas of ovarian stromal cells mixed in with the immature testicular cells. He concluded that these gonads were ovotestes. None of the other authors have considered the gonads to be ovotestes or to be other than immature testes. If it should be that these gonads actually are ovotestes as Novak thought, then these persons are true hermaphrodites. Howard [9] placed these patients in one class, which he termed adenoma tubulare group, because he described the gonads as being neither ovaries nor testes. He pointed out that the term was somewhat misleading because the peculiar gonadal structures are not necessarily neoplastic.

It is very likely that the three children reported in this paper fall into this unusual group of intersexuals. Each has a rudimentary vaginal canal and no cervix, uterus, tubes, or ovaries, and each has immature testes. Each had inguinal hernia. Of course they are not old enough to have developed axillary or pubic hair, mature breasts or libido; so these features cannot be recorded until the children have reached maturity.

Two of the children are siblings. Extensive questioning of the two families uncovered no significant abnormalities of sex development in the family background.

Any surgeon who contemplates operating upon an apparent female child with inguinal hernia might encounter this same problem. It behooves him to examine the external genitalia very closely and to do a digital rectal examination in an attempt to palpate an infantile uterus or prostate. A gonad in the inguinal canal probably is an ovary if it reduces completely and stays reduced. A testis is less likely to reduce completely and stay reduced.

On the basis of the experience with these three cases a definite plan of action is advisable. At surgery any gonad found should be inspected very closely. If it is not a typical ovary a biopsy should be done, removing a fairly large wedge of tissue. The opposite inguinal canal should be opened, and if another gonad is found a biopsy should be done on it too. Frozen section might help make an immediate diagnosis, but it is essential to save enough tissue for permanent section. If there is any doubt about the child's sex, the peritoneal cavity should be opened at this time rather than subject the child to a later operation designed solely to determine its sex. A transverse incision in the skin fold over the internal inguinal ring is ideal for hernia repair. If it is necessary to enter the peritoneal cavity, incisions on each side are connected across the midline and the abdomen opened in the manner of a Pfannenstiel incision. Good exposure must be obtained for adequate visualization and palpation of the entire pelvis. It is important to establish the anatomical features of each case early in life so that intelligent consideration can be given to future problems.

A biopsy does not establish the histology of the entire gonad, but it is better than no biopsy. It is inadvisable to remove the gonad at the original operation in an attempt to settle the diagnosis, because there are probably hormonal growth factors which are not entirely understood as yet and which may be important in the development of the child whether it be male or female.

It is not possible to establish the sex of an individual definitely by hormone assay. The study of chromosomes in skin biopsies is a newer tool of apparent value, used by Moore, Graham, and Barr ‡ in establishing sex.

In a case of this kind the question arises as to how to raise the child. In each of these cases the parents were very insistent that the child be raised as a girl. Usually the parents have strong opinions in this regard. The majority of male pseudohermaphrodites are registered as females at birth and are reared as such. Howard [9] stated that psychic sexu-

‡ References 10 and 11.

ality is formed by the upbringing and the reaction of the individual to environment and to physical appearance rather than to any innate developmental process. The words of Hamblen and his co-authors [12] are worth quoting:

> The consensus at present is that individuals with gynecoid psychosexual desires and orientation should have these trends furthered by appropriate surgery and by estrogenization. This point of view is in striking contrast to one formerly held: ascertain the nature of the gonads and then fashion the individual as best possible to fit the gonadal sex regardless of the individual's wishes or possible psychosexual trauma. This surgical approach, although it is objective and academic, ignores environmental, social and psychological components. It results in far more traumatism to the majority of patients than the simple expedient of accepting the sex certified on the birth certificate and requiring that the individual conform to it.

It would be most difficult or impossible to construct a satisfactory phallus and scrotum with testes in any of the patients reported in this study. It would be unwise to try to do so, because these children may well develop physically, psychically, and socially as females. Providing that they do develop as females the question will arise at puberty or later whether or not to remove the testes. Apparently the testes do not cause any hormonal harm if left intact. However, if they are in the inguinal canal, they may be subject to trauma and may have to be removed because of discomfort. Nearly every patient with female physique lacking uterus, tubes, and ovaries and having no axillary or pubic hair has suffered from menopausal symptoms after gonadectomy. For this reason, it may not be advisable to do a gonadectomy upon these three patients when they reach puberty. These problems will require the careful consideration of endocrinologists and psychiatrists.

SUMMARY

Three children with female external genitalia and inguinal hernias containing immature testes have been presented. None of the children have female internal genitalia. Two of the children are siblings.

These three children may represent a special class of intersexuality characterized by female physique, female breasts and external genitalia, absent or scant axillary and pubic hair, and absence of uterus, tubes, and ovaries. Only time will determine whether these children fall into this special group.

Any surgeon who operates upon female children with hernias must view each patient as a possible male pseudohermaphrodite. Biopsy should be done on abnormal-appearing gonads, and they should not be removed. In doubtful cases the peritoneal cavity should be opened and the pelvis carefully inspected for internal genitalia at the time of the hernia repair.

Very serious attention should be given to the question of raising patients of this type as boys or girls. Consultation with psychiatrists and endocrinologists is advisable.

These cases have been presented in order to alert physicians to be on the lookout for cases of intersexuality in female infants with hernias and, in particular, to acquaint surgeons with the proper method of handling the problem at the time of operation.

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Benign Pharyngeal Erythema and Follicle Formation in the Newborn

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It is the purpose of this communication to bring to the attention of all concerned with the newborn infant a benign condition of his pharynx the recognition of which is important, since it may mimic potentially serious bacterial or viral infections.

Our attention was first directed to this condition on Sept. 15, 1954, when an infant in the newborn nursery at the North Shore Hospital was found, during a routine physical examination on the third day of life, to have an unusual looking pharynx. It was described by his pediatrician, Dr. Charles Leslie, as consisting of "four to five whitish-yellow papulovesicles on the tonsillar pillars and soft palate, typical of herpangina seen in older children." Although the child did not present any unusual symptoms, he was isolated and his throat cultured. The throats of all the other infants in the two nurseries in use at the time were examined and cultured, as were the throats of the professional personnel of the nurseries and delivery room. Three other infants—out of a nursery population of 17—were also found to have somewhat similar, though less severe throat lesions. These babies were also free of related symptoms. Preliminary observation of the throat cultures after six to eight hours indicated the presence of long-chained cocci. Therefore all the infants were given two daily injections of procaine penicillin. The cocci were later identified as α-hemolytic streptococci. No new cases appeared, and all except the original child were discharged at the usual time, on the fifth day of life. This baby was continued on penicillin for two more days. At that time his throat appeared only slightly red, and he was sent home. Approximately two weeks later, on Oct. 2, 1954, another instance of what was thought to be follicular pharyngitis was again accidentally observed. At this time a systematic daily inspection of the throats of all full-term newborn infants was undertaken. Typical pharyngeal lesions were seen in approximately 20% of the infants during the following four months. The remainder of this report will be concerned with a description of the lesions and preliminary studies which were undertaken to determine their nature and significance.

Submitted for publication Sept. 28, 1955.

From the Division of Pediatrics, North Shore Hospital.

Read by title and presented in abstract at combined meeting of the American Pediatric Society, the British Paediatric Association, The Society for Pediatric Research, and the Canadian Paediatric Society at Quebec, June 15-18, 1955.

THE PHARYNGEAL LESION

The characteristic lesion was seen on one or both of the anterior tonsillar pillars (the glossopalatine arches). It consisted of one to three slightly elevated discrete white to yellow circular areas about 1 mm. in diameter which were on an erythematous base (Fig. 1). These might increase in size and number the following day. Then in one or two days the elevated areas disappeared, and all that remained was a general erythema. Sometimes the elevated areas were replaced by shallow ulcers. These were usually oval or irregular in shape and never more than 1 to 3 mm. in their widest diameter. Ap-

proximately three days after the lesions were first observed the pharynx appeared to be normal.

These lesions were occasionally seen as early as the day of birth and as late as the fifth day of life, which incidentally was usually the day of discharge and consequently the last day for observation. However, they were most frequently found on the second and third days of life (Table 1).

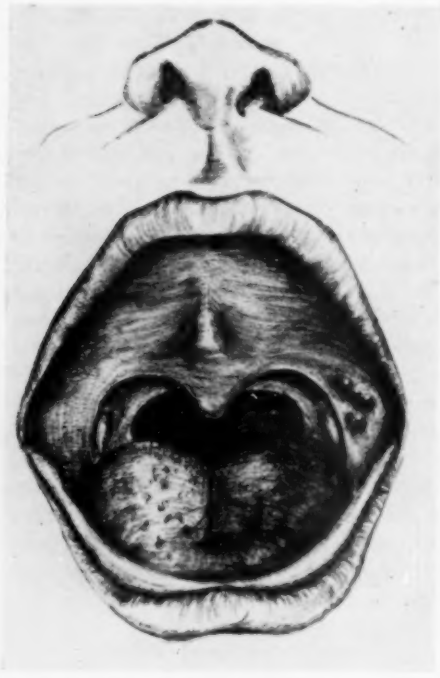

Fig. 1.—Sketch showing frequent appearance and site of pharyngeal lesions.

These pharyngeal lesions had never been noticed before by us and were thought at first to be a new observation. As our study progressed a description of what are probably the same lesions was found under the name "transitory spots on the palate" in von Reuss' book, "Diseases of the Newborn," published in 1922.[1]

TABLE 1.—*Day of Life When Follicles Were First Found in Sixty Infants with Lesions*

Day of Birth	1st Day	2d Day	3d Day	4th Day	5th Day
2	4	25	26	2	1

Benign Clinical Picture.—The pharyngeal lesions appeared to be benign. The temperature, feeding habits, weight curves, and stool patterns of infants with the lesions did not differ from those without them. In a few instances leucocyte counts were taken on these infants, and these too did not differ from the normal.

Frequency.—During the four-month period from October, 1954, through January, 1955, almost daily observations were made of the throats of all full-term infants born at the North Shore Hospital. In this way 78 instances of pharyngeal lesions were found among 347 babies (approximately 20% of the total). Only those infants whose lesions could be seen on two consecutive days were considered. The distribution of these cases is shown in Figure 2. It will be seen that there were more than twice as many instances of these unusual throats seen during December as during October—31 as compared to 14. Nevertheless, the total number of nursery discharges in both months were approximately the same. There were 99 discharges in December and 91 in October. This increased incidence might have been due to chance, but it also would be consistant with the presence of an infectious agent, especially since no effort was made to isolate these patients after the first few weeks, when the benign nature of the lesions seemed clear.

Etiology.—Our first studies were directed at finding an infectious etiology. These have so far been limited.

Bacterial cultures were made by swabbing throats with sterile cotton swabs which were placed in tubes of brain-heart infusion broth (Difco), incubated for several hours at 37 C, and then plated out on rabbit or sheep-blood agar.

As already indicated, when the original case was discovered bacterial cultures were taken on the entire nursery population. The four infants with pharyngeal lesions had

Fig. 2.—Occurrence of cases during period of October, 1954, through January, 1955.

predominantly α-streptococci (90% to 100% of the colonies) and a small number of staphylococci and Neisseria catarrhalis. The throats of the 13 infants without lesions also contained a predominance of α-streptococci. Subsequently bacterial cultures were taken on a number of infants with these lesions with very much the same results. Alpha-streptococci, staphylococci, and coli-aerogenes organisms were usually found. On only two occasions were β-hemolytic streptococci reported, and these were not in Group A. These results are considered to be consistent with what has been reported by Torrey and Reese [2] as the normal throat flora in the neonatal period.

Viral studies which so far must be considered as only the most superficial kind of survey have been carried out with the cooperation of Dr. Walter Henley and Miss Helen Zepp, of the Mount Sinai Hospital. Throat swabs from 13 infants with throat lesions were put into tubes containing 10% horse serum and frozen at approximately —10 C. Subsequently this material was pooled and inoculated into several litters of suckling mice and into several roller tubes of monkey-kidney tissue without producing significant changes.

Another possible cause for the throat lesions was thought to be the trauma of pharyngeal suction which is so frequently employed immediately following delivery. To investigate this possibility a careful record was kept during several months of the type and frequency of suction employed. This was done with the cooperation of the anesthesiologists (who at the North Shore Hospital are responsible for the resuscitation of all newborn infants) and the delivery-room and nursery nurses. This information was put on each infant's chart when he was transferred from the delivary room to the nursery and in the nurses' notes if he was suctioned in the nursery. It was found that although a variety of suction facilities were available, a rubber ear bulb was used most frequently. The suction furnished by these bulbs may be considerable, depending upon

TABLE 2.—*Presence of Follicles in Relation to Pharyngeal Suction Following Delivery*

		Number of Times Suction Applied							
		0	1	2	3	4	5	6	7	8
Infants with follicles....	33	4	2	9	6	6	2	4	..	..
Infants without follicles	43	5	7	7	3	10	3	3	1	4
Total.....	76									

the age of the rubber and enthusiasm of the operator.

Good records were available on 76 infants who had been suctioned with a rubber bulb at the time of delivery and who as far as could be determined did not receive further suction in the nursery. In Table 2 there is summarized an attempt to correlate the appearance of lesions with the amount of suction. The lack of correlation is apparent. Although this does not completely eliminate the possibility that mechanical trauma might play a role in the formation of these lesions, it suggests that it cannot be a major role.

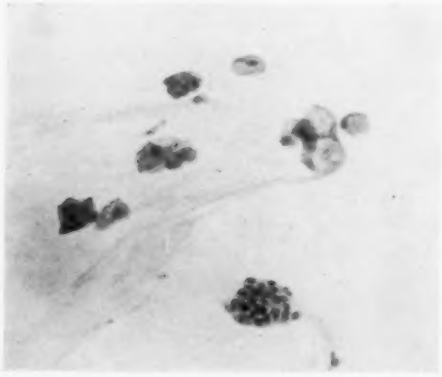

Fig. 3.—Pharyngeal smear from infant with typical lesions, showing characteristic cluster of epithelial cells with scanty cytoplasm and absence of inflammatory reaction.

Cytology.—The cytology of the pharynx of these infants was also studied. Pharyngeal smears were made with cotton swabs onto glass slides, which were immediately fixed in alcohol and ether and later stained with the Papanicolaou technique. The limitations of this approach are many and include the fact that in swabbing the area, normal as well as abnormal surface cells are removed. Nevertheless, our preliminary observations have been most interesting. From the control, or normal, infants' throats we obtained only old squamous cells with small nuclei and large amounts of cytoplasm. From the throats of infants with typical lesions many of these same squamous cells were obtained, but in addition there were found varying numbers of clusters of cells with slightly larger nuclei and smaller amounts of cytoplasm. (Fig. 3). In none of these typical cases was more than an occasional polymorphonuclear or inflammatory cell found. The significance of these observations is still under study. It appears, however, that the cells which are found in the clusters resemble the deeper epithelial cells of pharyngeal mucosa. This suggests that the pharyngeal lesions may represent follicles or small sacs of deeper cells which for some as yet unexplained reason have been extruded to the surface. We have therefore used the phrase "benign pharyngeal erythema and follicle formation in the newborn" for these lesions to indicate their benign clinical course, appearance, and possible pathology.

COMMENT

Inspection of the throat of the newborn infant is usually not easy. However, if his head is firmly held by the nurse and a small narrow tongue blade pushed in and down as far back as possible, a good view of the pharynx can usually be obtained with the aid of a bright light. It is known that the buccal membranes of the newborn, especially those of the palate, vary greatly in vascularity. Indeed, erythmea of the throat in this age group is usually considered physiological and similar to the erythema of the skin. It is therefore not surprising that relatively little attention has been paid to the appearance of the throat of the newborn infant. However, when white follicles or ulcers are seen in this area, they cannot fail to excite interest. When our attention was first directed to this condtion we could not recall ever having seen quite the same picture. Perhaps this was a reflection of the custom of examining newborn infants on

the day of birth and again on the day of discharge from the nursery, which is usually the fifth or sixth day of life, as well as of the difficulty of examining the pharynx in these young infants. As indicated in Table 1, these would be the least likely days on which to find lesions. Inquiry among our older colleagues also indicated a lack of familiarity with this lesion. However, Dr. Bela Schick did recall having read of something similar and led us to find the already mentioned account of "transitory white spots on the palate" in von Reuss' book.[1]

Von Reuss' description and comments are worthy of direct quotation:

> In the first days of life curious irregularly shaped spots frequently appear on the palate. They are sometimes circular, sometimes more jagged and lie either near the raphe on the boundary between the hard and the soft palate, or near the corners of the palate on one or on both sides. Originally delicate greyish-white with indistinct margins, they soon assume a more definite form. Their margins are then bright red and sometime hemorrhagic. The mucous membrane in the center of the spot is anemic, often yellowish as the result of commencing icterus; on closer examination a shiny skin-like layer may be seen which may easily be removed with a spatula; on the anemic mucous membrane, which has been exposed, small punctate hemorrhages may sometimes be seen. These spots on the palate are not visible on the first day, and do not, as a rule, appear until the second to the fourth day, they increase at first in intensity and then rapidly fade away. They have usually disappeared entirely by the end of the first week. The phenomenon is usually perfectly harmless. It has not been disproved that these spots may now and then cause pain during suckling, but as a rule, they do not appear to cause any difficulties. The possibility of an infection is naturally not excluded. It has not quite been ascertained to what this loss of substance is due. It is possibly connected with the wiping out of the mouth which is usually done by the midwife immediately after the birth of the child. . . .

This description sounds very much like what we saw—except that our infants had lesions which seemed to be elevated, and their surface could not be wiped away easily. Otherwise, the location, time of appearance, and time of disappearance seem similar in the two instances. Our investigation of these lesions failed to support von Reuss' thesis that they are the result of trauma. In our delivery room actual wiping out of the mouth is rarely employed, although suction with a rubber bulb is very frequent. In Table 2 we have summarized our observations, which do not show any correlation between the trauma of suction and the appearance of pharyngeal follicles. Von Reuss could not exclude the possibility of infection and neither can we, although we have probably excluded the possibility of infection by one of the usual aerobic bacteria. As yet we can say very little about the possibility of viral agents being responsible. The observation that inflammatory cells were absent from pharyngeal smears of these infants is not inconsistent with a viral etiology. Adams, in describing pharyngeal smears from infants with primary pneumonitis [5]—which is presumably due to a virus and influenza [6]—comments about the striking absence of polymorphonuclear leucocytes. It should also be recalled that the viruses of molluscum contagiosum and warts produce proliferative lesions without any inflammatory reaction. However, because the lesions were occasionally found on the first day of life, an intrauterine infection would have be be supposed.

Perhaps the most practical and interesting information was obtained from the cells in the pharyngeal smears. The technique is simple, and the absence of a predominance of polymorphonuclear cells and bacteria quickly confirms the absence of significant bacterial infection. For routine use in differential diagnosis, a simple Wright's stain may replace the Papanicolaou. The Papanicolaou stain, however, did seem to suggest a possible etiology for these lesions. When some of these slides were shown to Dr. Donald Gribitz, he commented on the similarity of cells seen in smears made from the throats of our patients and those seen in vaginal smears made during estrogen withdrawal. This similarity and the known fact that during the first few days of life the newborn infant is actively undergoing estrogen withdrawal [8] suggested the possibility that the pharynx of the newborn might also be a "target area" for estrogen-withdrawal effect. This possibility is being studied.

The pharyngeal lesions described in this report are readily distinguished from epithelial pearls, or Bohn nodules, which are also white or yellow. Epithelial pearls are seen at birth, usually in or near the raphe of the hard palate in groups of two to four. In size and appearance they have been said to resemble fine specks of gravel pushed under the mucous membrane,[1] and they rarely have an erythematous base. Similar formations are also seen in the gums. They are said to be present in 90% of all newborn infants and to be small retention cysts of the mucous glands. They usually disappear spontaneously. Bednar's, or palatal-angle, ulcers must also be differentiated. They are said to appear later than the epithelial nodules, being found in infants 1 to 2 weeks old. We have never encountered this lesion, but it is reported to be in its typical form an elongated and oval spot about the size of a lentil, which is surrounded by a red border. According to Epstein, cited by von Reuss, it occurs after the mucous membrane has been injured by too vigorous cleansing of the mouth and secondarily infected.[1]

It should be stressed that infants with pharyngeal erythema and follicles are not obviously ill. The clinical importance of this condition lies in recognizing and differentiating it from potentially more serious throat infections during the newborn period. Abramson [6] has pointed out that newborn infants are vulnerable to acute respiratory ailments. In his study of several outbreaks of respiratory infection in New York City nurseries, he found that although most of the infected infants had fever and pneumonia a few had only a pharyngitis.

SUMMARY

The condition of benign pharyngeal erythema and follicle formation in the newborn is described. It characteristically consists of several small white or yellow follicles or ulcers on an erythematous base, which are found on the second or third day of life on the anterior tonsillar pillars. The lesions clear in two or four days. The infants do not appear to be ill.

During a four-month period it was seen in the throats of 20% of all the full-term infants in our nursery.

The etiology is unknown. The possibilities of trauma, infection, and estrogen withdrawal were considered as causative factors. The trauma of postdelivery pharyngeal suction seems to have been excluded. Only preliminary bacteriological and virological studies have been carried out. So far they have been negative. Endocrine studies have just been started.

Pharyngeal smears from infants with these lesions show a characteristic cluster arrangement of cells and a striking absence of inflammatory cells. These smears may serve as a practical means of differentiating this benign condition from more serious pharyngeal lesions which it may mimic.

Dorothy Dreves, R.N., and her nursery staff cooperated in this study, and Liljan Wunderman made the sketch shown as Figure 1.

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Glomerulonephritis in Miami, Florida

Studies on Types 12, 4, and Red Lake Group A Beta-Hemolytic Streptococci Isolated over a Three-Year Period (1953-1955)

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Evidence has been accumulating that acute hemorrhagic glomerulonephritis may occur as a nonsuppurative complication following infection with some strains of certain types of Group A β-hemolytic streptococci. Types 12 and 4, especially, have been implicated in this way,[1] although it is recognized that not all strains of these types are nephritogenic.[2] Other types [3] also have been found to produce nephritis. A new type was recently isolated in an epidemic at Red Lake, Minn.*

Many strains of Types 12, 4, and Red Lake were isolated from the throats of school children during a long-term study of the streptococcal epidemiologic pattern in Miami, Fla.† We therefore tried to evaluate these findings in relation to the incidence of nephritis in this area.

Received for publication Oct. 24, 1955.

From the Department of Medical Research, National Children's Cardiac Hospital and the University of Miami School of Medicine.

Supported in part by funds from the Florida State Board of Health and grant H1738, U. S. Public Health Service, with the cooperation of the Dade County Board of Public Instruction, the Dade County Board of Health, the Florida State Board of Health, and the U. S. Public Health Service.

* References 4 and 5.

† References 6 and 7; Saslaw, M. S., and Streitfeld, M. M.: The Role of Group A Beta Hemolytic Streptococci in the Pathogenesis of Rheumatic Fever in Miami, Fla., read before the 28th Annual Scientific Sessions of the American Heart Association, New Orleans, Oct. 24, 1955.

MATERIAL AND METHODS

From February through May, 1953, from October, 1953, through May, 1954, and from October, 1954, through May, 1955, pairs of throat swabs were taken monthly from an average of 315 children attending Grades 1, 2, and 3 in three schools in Miami, Fla. In all, 6400 pairs of throat swabs were taken from a total of 740 children.

The method of collecting, incubating, isolating, and subculturing of the throat cultures has been described previously.‡ One swab was streaked directly on a plate of Difco blood agar base, and the other, on a plate of Difco neopeptone heart infusion agar, each of which was enriched with 4% defibrinated sheep's blood. All isolated cultures were grouped by standard agglutination techniques and typed by Lancefield's precipitin method at the Streptococcus Laboratory, Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare, Chamblee, Ga.

Streptococci containing Type 12 M protein, as identified by the Lancefield precipitin method, may contain either Type 10 or Type 12 T protein.[8] Therefore all strains identified as Type 12 by Lancefield's precipitin technique were further tested against Griffith's Types 10 and 12 agglutinating sera to differentiate strains containing each of the two types of T protein. These sera were supplied by Dr. R. E. O. Williams, Streptococcus Reference Laboratory, Public Health Laboratory Service, Colindale, London.

As controls, 19 strains of Group A β-hemolytic streptococci isolated from patients ill with nephritis were supplied by Dr. Elaine L. Updyke, Streptococcus Laboratory, Communicable Disease Center, Chamblee, Ga. Two of these were known to contain Type 10 T protein, and the remainder, Type 12 T protein. Five "nephritogenic" Lancefield Type 12 strains, supplied by Dr. Charles Rammelkamp Jr., Western Reserve University, Cleveland, also were tested with the Griffith sera.

‡ References 6 and 7.

Cultures were prepared for Griffith's slide agglutination tests [9] by a method devised in our laboratory,[10] in which commercially available trypticase soy broth (B. B. L.) was used and cultures were prepared by 24-hour incubation at room temperature.

To determine the prevalence of clinical nephritis in Dade County, Fla., we obtained information from the following sources:

1. Parents were canvassed to obtain a record of previous illness, especially referable to the kidney, in each of the children from whom Type 12, Type 4, or the Red Lake type of Streptococcus had been isolated.

TABLE 1.—*Isolation of Types 12, 4, and Red Lake Group A β-Hemolytic Streptococci from Miami School Children, 1953-1955*

	Year of Study			
	1953	1953-1954	1954-1955	Total
Children from whom cultures were taken, no.				
New children	343	231	166	740
Carried over from previous year	...	186	167	353
Total children	343	417	333	1,093
Type 12				
Children, no.	25	13*	5†	36
Strains, no.	34	32	29	95
Type 4				
Children, no.	0	8	19‡	25
Strains, no.	0	10	72	82
Red Lake§				
Children, no.	...	...	2	2
Strains, no.	...	...	10	10
Total Types 12, 4, and Red Lake				
Children, no.	25	21*	26†‡	63
Strains, no.	34	42	111	187
All other Group A				
Children, no.	22	105	111	238
Strains, no.	25	183	234	442
Total cultures taken, no.	1,154	2,809	2,437	6,400

* Includes six children carried over from previous year.
† Includes one child positive during previous two years.
‡ Includes two children positive during previous year.
§ First reported in 1955.

2. Records of the five hospitals handling such cases in the area were checked for the number of patients with nephritis admitted between Jan. 1, 1950, and April 30, 1955.

3. Twenty-five practicing pediatricians (approximately half of those in this area) were questioned as to the number of children with nephritis seen by them during the past three years.

RESULTS

Table 1 shows the isolation of Types 12, 4, and Red Lake from the children studied. A total of 187 of these strains were recovered from the throats of 63 children. In addition, 442 other nontypable and typable strains of Group A β-hemolytic streptococci were isolated from 238 children; the typable strains included Types 1, 3, 6, 11, 13, 23, 28, 31, 33, 39, 43, and 44.§

Tables 2 and 3 indicate the persistence of Types 12, 4, and Red Lake from year to year during the three-year study period. Of the 25 children who harbored Type 12 strains during February through May, 1953, there were 14 not included in the October, 1953, through May, 1954, study, either because they had moved away from the school or

TABLE 2.—*Persistence of Types 12, 4, and Red Lake in Sixty-Three Children, 1953-1955*

	Type 12	Type 4	Type Red Lake
Total children with positive cultures	36	25	2
1-year participant	17	15	2
2-year participant	8	10	..
3-year participant	11	0	..
Total 2- and 3-year participants	19	10	..
Positive 1 year only	9	8	..
Positive 2 years	9*	2*	..
Positive 3 years	1*	0	..

* See Table 3.

TABLE 3.—*Group A β-Hemolytic Streptococci in Twelve Children with Persistent Types 12 and 4* *

Case	1953	1953-1954	1954-1955
1	A_{12}	A_{12}	Not in study
2	A_{12}	Negative	A_o
3	A_{12}	A_{12}	Not in study
4	A_{12}	Negative	A_o & Group C
5	A_{12}	A_{12}	Negative
6	A_{12}	A_{12}	Not in study
7	A_{12}	A_{12}	A_o
8	Negative	A_{12}	A_o
9	Not in study	A_{12}	A_o
10	A_{12}	A_{12}	A_{12}
11	Negative	A_4	A_4
12	Negative	A_4	A_4

* A_{12}, Type 12; A_4, Type 4; A_o, nontypable Group A.

§ References 8 and 9; Saslaw, M. S., and Streitfeld, M. M.: The Role of Group A Beta Hemolytic Streptococci in the Pathogenesis of Rheumatic Fever in Miami, Fla., read before the 28th Annual Scientific Sessions of the American Heart Association, New Orleans, Oct. 24, 1955.

because their parents refused to have them continue in the study. Of the remaining 11 children, 6 continued to carry Type 12 in their throats during the second study. Only one child harbored Type 12 throughout the three-year period. Except for this case, no other child showed Type 12 persisting from the second to the third year of study.

Table 4 shows the response to Types 10 and 12 Griffith's agglutinating sera of the 65 Type 12 strains isolated by us during October, 1953, through May, 1954, and those strains supplied by Drs. Updyke and Rammelkamp. None of our 65 strains agglutinated with Type 10 Griffith's serum. One strain (1113 LI) failed to react with either Type 10 or Type 12 serum (owing to the loss of T-protein?). However, two other cultures from the same child (1113 MN and 1113 NI) gave agglutination with Type 12 serum. None of the five nephritogenic strains supplied by Dr. Rammelkamp agglutinated with Type 10 serum. Of the strains supplied by Dr. Updyke, only two reacted with Type 10 Griffith's serum.

Follow-up medical data were available in 56 of the 63 children. In not a single instance was there evidence of either serious illness or any history suggestive of clinically recognizable glomerulonephritis.

Table 5 lists the number of cases of acute and subacute glomerulonephritis in children and adults hospitalized in Dade County, Fla., between 1950 and 1955.

The 25 pediatricians canvassed reported a total of 76 cases of glomerulonephritis in children during the period 1952 through 1954; 40 had received treatment at one of the five hospitals listed in Table 5. Thus, the pediatricians recorded 36 additional cases in three years. The number of cases reported by each physician individually varied from 0 to 10 for the three-year period. The public school population has been between 75,000 and 100,000 for each of the three years; the approximate total population of Dade County, 650,000.

TABLE 4.—*Response to Griffith's Types 10 and 12 Agglutinating Sera of Lancefield Type 12 Strains Isolated from Miami School Children, October, 1953-May, 1954: Comparison with Strains Isolated from Patients with Glomerulonephritis*

Investigators	Type 12 Strains (Lancefield), No.	Response to Griffith's Agglutinating Sera, Strains, No.		
		Type 10	Type 12	No Response to Types 10 or 12
Updyke	18 from glomerulonephritis cases ("nephritogenic")	1	16	1
	1 control (Type 10T)	1	..	..
Rammelkamp	5 from glomerulonephritis cases ("nephritogenic")	0	4	1
Streitfeld, Saslaw, and Doff [7]	65 (Oct., 1953-May, 1954)	0	64	1 (1113 LI)
Total	89	2	84	3

TABLE 5.—*Hospitalized Cases of Acute and Subacute Glomerulonephritis in Dade County, Fla. (1950-1955)*

Hospital	Cases, No.	Dates	Case Rate/Mo.
J. M. H.	46	January, 1950, through April, 1954	0.88
V. C. H.	39	December, 1950, through April, 1955	0.75
S. F. H.	4	1950 through 1954	0.06
M. S. H.	9	1948 through June, 1954	0.14
D. C. H.	13	1950 through 1954	0.22
Total	111	1950 through 1955	0.38

COMMENT

The absence of glomerulonephritis among the children from whom Types 12, 4, and Red Lake β-hemolytic streptococci were isolated supports the generally accepted concept that not all strains of these types are nephritogenic. Although Type 12 organisms have been most commonly implicated, Wertheim and co-workers [11] concluded that "data already at hand indicate that the Type 12 hemolytic streptococcus is quite variable in its ability to initiate acute glomerulonephritis."

Infections with strains of other types also have been known to be followed by nephritis.‖ It is therefore noteworthy that none of the children from whom Types 1, 3, 6, 11, 13, 23, 28, 31, 33, 39, 43, and 44 were isolated between February, 1953, and May, 1955, developed clinical glomerulonephritis or any other severe streptococcal illness. Thus, it is obvious that the rate of occurrence of nephritis cannot be predicted solely on the basis of the number of children harboring streptococci.

In 1951, Lange and his associates [12] summarized the historical background of the hypothesis that clinical glomerulonephritis is a manifestation of an antigen-antibody reaction. In this reaction, some nephrotoxic factor probably produced by certain strains of β-hemolytic streptococci combines with kidney protein, rendering it antigenic so that it may stimulate the formation of specific antibody, which reacts with the altered kidney to produce glomerulonephritis. Recently, Reed and Matheson ¶ reported experimental induction of kidney lesions in rabbits following localized infections with subcutaneous injections of whole cultures or intravenous injections of filtrates of the same cultures of Type 12 streptococci isolated from patients with glomerulonephritis during an epidemic of this disease. They speculated that their data were not inconsistent with the antigen-antibody theory of the pathogenesis of glomerulonephritis.[14]

‖ References 3-5.

¶ References 13 and 14.

Another possible explanation for the occurrence of clinical glomerulonephritis may lie in the Shwartzman phenomenon. Thomas,[16] in studies of the generalized Shwartzman reaction, has indicated that "a streptococcal infection, in rabbits, can result in a profound alteration in the susceptibility of the heart, kidney, and other tissues to damage by bacterial endotoxins [from certain Gram-negative organisms] which would cause no ill effects in normal, uninfected animals."

The infrequency of nephritis in Dade County, Fla., may be due to some alteration (1) in the streptococcal strains recovered, with resultant interference in the production of nephrotoxic factor, or (2) in the host reaction to such a factor, possibly influenced by the "tropical" [16] climate of this area.

Although Seegal, Seegal, and Jost [17] have reported that glomerulonephritis appears to be as common in the South as in the North, we have observed that nephritis (like rheumatic fever [18]) is infrequent in Dade County, Fla. Hospital records and physicians' reports corroborate these findings. Thus, climate may be a factor in the low incidence of nephritis, especially in the South.

A third possible explanation for this low incidence may be the necessity for the presence of a virus concomitant with a β-hemolytic Streptococcus. A disease resembling, and possibly identical with, acute glomerulonephritis was produced experimentally in monkeys by combined injections of Group C streptococci isolated from a case of human scarlet fever and influenza virus A.[19] Injection of either the virus or the Streptococcus alone failed to produce kidney lesions. This work poses the very interesting possibility that strains of both Group C and Group A β-hemolytic streptococci may contain a nephrotoxic factor. In our study, we found no clinical evidence of nephritogenicity among 44 children from whom Group C streptococci were isolated during 1954-1955.

Thus our data are compatible with the suggestion [1] that variability in attack rate

of nephritis may be related to greater nephritogenicity of some streptococcal strains than others. We are not convinced, however, that the attack rate "apparently is not influenced by host susceptibility or geographic and climatic factors." [20] We feel that geographic and climatic factors may affect the etiologic agent, the host, or the relationship between the two and thus directly or indirectly may be responsible for the low incidence of nephritis in Dade County, Fla.

SUMMARY

From February, 1953, through May, 1955, a total of 187 strains of Lancefield Types 12 (95 strains), 4 (82 strains), and Red Lake (10 strains) Group A β-hemolytic streptococci were recovered from the throats of 63 children. These strains were isolated from 6400 pairs of throat cultures taken from 740 children attending the first three grades in three Dade County, Fla., public schools.

Despite the association of the above types of Group A β-hemolytic streptococci with epidemic glomerulonephritis reported by others, none of the children in our study developed clinical nephritis.

Eleven additional types of Group A streptococci were isolated from the throats of 238 of the 740 children (442 strains). None of these children developed overt nephritis.

Local hospital records, as well as a canvass of practicing pediatricians, gave further evidence of the infrequent occurrence of nephritis in Miami, Fla.

Griffith agglutination tests performed on all strains of Type 12 streptococci isolated in this study showed that these organisms contained T 12, as well as M 12, protein (not T 10, M 12).

Although it is recognized that different types and strains of streptococci display a variable attack rate for nephritis, the possible influences of geographic and climatic factors on the organism, the host, and/or their relationship are discussed.

Miss Alba Colon and Mrs. Nettie K. Cudequest gave technical assistance.

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Blood Transfusion by the Intraperitoneal Route

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In the adaptation of new procedures and techniques in medical therapy there is a tendency to abandon or overlook an occasional therapeutic aid which has proved of value in the past. The case here presented illustrates the use of such a technique which we believe is ideal in the situation under discussion.

The patient was a child with thalassemia major (Mediterranian anemia, Cooley's anemia, erythroblastic anemia) in whom repeated transfusions were necessary. Eventually as a result of this and because of the age of the patient, her obesity, and the extremely low hemoglobin, together with decreased peripheral circulation, each succeeding transfusion became more and more of an ordeal, to the patient, to the parents, and to the physician, until a point was reached at which such transfusions were no longer technically possible. Superior saggital sinus transfusion might have been done, but this is not without danger and requires considerable experience and a high degree of technical skill. Bone marrow transfusion was also considered, but this, also, we did not feel was highly practical in cases such as this, where repeated transfusions are indicated. The problem was brought to the attention of one of us (J. G.), and intraperitoneal transfusion was suggested.

Submitted for publication Oct. 14, 1955.

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This procedure, while not currently in general usage (it had not been done in this hospital for at least 20 years), appeared to offer a number of advantages. It is easy to perform, is quickly accomplished with very simple equipment, and does not endanger or noticeably discomfort the patient. It is a simple office procedure which can also be used under conditions such as military situations, where lack of equipment, trained help, and time might be important factors.

The investigation of the absorption of fluids and particles from the peritoneal cavity dates back to von Recklinhausen,[1] who studied this problem in 1862. MacCallum [2] and Florey [3] demonstrated the presence of minute openings in the diaphragm which presumably opened and closed with respiration. Allen [6] and Allen and Vogt [7] later showed that these openings, termed "stomata," opened and closed with movements of the diaphragm and would permit the passage of particles 2μ to 20μ in diameter into the lymphatics. The ultimate absorption of such particles into the blood stream was due to this and not to phagocytosis.

Siperstein and Sansby,[4] in 1923, presented a comprehensive review of the literature of the subject and successfully gave rabbits intraperitoneal transfusions of fresh, citrated whole blood. It was shown that a rabbit could absorb approximately one-fifth of its own blood volume in four hours. Siperstein,[5] shortly thereafter, successfully gave a series of infants and children intraperitoneal transfusions. Subsequently Clausen [8] employed differential agglutination to demonstrate the presence of intraperitoneally transfused red cells in the peripheral circulation. Hahn and associates,[9] in studies on dogs, used red blood cells tagged with radioactive iron to study peritoneal absorption and demonstrated by autopsy studies that all the serosal surfaces

took part in the absorption of the red cells. They described the filling of the anterior mediastinal lymphatics with lymph and erythrocytes and commented upon the absence of phagocytosis as the cells passed through the lymph nodes. In 1947, Hedenstedt [10] used elliptocytes and gave intraperitoneal transfusions to 31 children ranging in age from 8 days to 13 years. He demonstrated the survival time of the elliptocytes to be the same as when given by intravenous transfusion. McKee and Stewart,[11] working with dogs, showed approximately 50% absorption in 72 hours, although absorption may continue for more than one week.*

TECHNIQUE OF INTRAPERITONEAL TRANSFUSION

Blood which has been typed and cross matched against the patient's cells and serum is prepared in the same manner as for intravenous transfusion. The filter tube leading to the bottle is attached to a three-way stopcock to which is attached a 20 cc. syringe and also a tube leading to a No. 20 needle, the point of which is not needle sharp. The syringe and the tubes are filled with sterile isotonic saline solution.

After restraining the patient in the supine position and carefully palpating and percussing the abdomen to delineate the size and position of the liver, spleen, and bladder, the child is prepared as for abdominal paracentesis. In the absence of contraindications, such as large organs or masses, the needle is introduced at either lateral margin of the rectus abdominis muscle, about midway between the level of the umbilicus and the symphysis pubis. In our particular case of thalassemia major it was necessary to introduce the needle into the right side of the abdomen to avoid puncturing the enlarged spleen.

When the needle is in the peritoneal cavity, the saline solution may be easily injected without resistance, and no saline will be recovered on aspiration with the syringe if only enough is injected to determine the patency of the needle and the fact that it is free in the peritoneal cavity. The remaining saline solution is then discarded and the blood introduced by alternately drawing it into the syringe and discharging into the peritoneal cavity (Fig. 1).

After the required amount of blood has been injected, the needle is withdrawn and the puncture covered with a dry, sterile dressing. If the patient is restless a sedative is given or he is restrained. The patient is then observed for a period up to 12 hours (particularly with respect to melena) and discharged, unless complications, which are rare, have occurred.

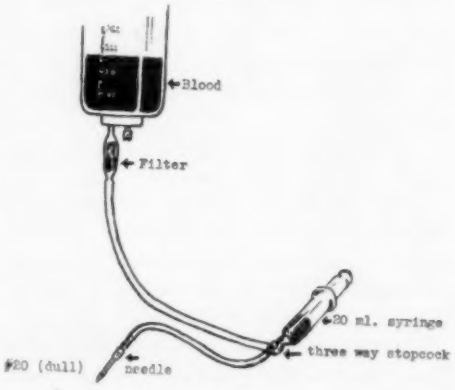

Figure 1

REPORT OF A CASE

The patient, a white baby girl, was first admitted to Genesee Hospital at the age of 4 months because of "dropping blood count." One month prior to admission one of us (D. D. C.) had noticed pallor during a routine physical examination. There had been no evidence of illness prior to this date. A daily iron supplement was administered for a month. Two days prior to admission the hemoglobin was reported as 7.1 gm. per 100 cc. (Sahli). On admission for more exhaustive studies the patient was found to be well developed and nourished but pale, with a yellowish tint to the skin. A firm, rather rubbery splenic edge was felt 3.5 cm. below the costal margin. A small umbilical hernia was present, and the mucous membranes appeared pale. No other gross abnormalities were found.

Laboratory studies done during the two days following admission showed a microcytic, hypochromic anemia with an elevated reticulocyte count (9%) and abnormal red-cell fragility. The con-

* References 9 and 10.

sulting pediatric hematologist, Dr. Gerald Miller, reported that the laboratory findings were consistent with thalassemia major, and blood studies on both parents were consistent with thalassemia minor.

The third day following admission the hemoglobin was reported as 5.2 gm. per 100 cc. (Sahli). Intravenous transfusions of 110 cc. each of citrated whole blood were given on two successive days, and two days later the hemoglobin was reported as 14.4 gm. per 100 cc. (Sahli) and the hematocrit 42% (micromethod) and she was discharged from the hospital.

Thereafter the child was given intravenous transfusions, with successively increasing technical difficulties, at the ages of 5½, 7, and 9 months. It was then found to be impossible to give intravenous transfusions through the ordinary superficial veins or those on which cutdowns are commonly made. Therefore, at the age of 10 months she was given 130 cc. of citrated whole blood intraperitoneally and two days later another 100 cc. in the same manner. After these procedures the hemoglobin and hematocrit values rose steadily to a high of 13.6 gm. per 100 cc. of hemoglobin (Sahli) noted 10 days after the last intraperitoneal transfusion. The patient tolerated the procedure well and showed no evidence of any change in the vital signs or any evidence of distress. It was, however, noted after the first transfusion that the umbilical hernia had a bluish tinge (Cullen's sign: umbilical or periumbilical darkening of the skin in intraperitoneal hemorrhage).

The patient returned to the hospital two months later, at the age of one year, with a hemoglobin value of 6.2 gm. per 100 cc. (Sahli) and was again given an intraperitoneal transfusion with 100 cc. of citrated whole blood. Since then, up to the time of this writing, (age 17 months), she has had six intraperitoneal transfusions, always with highly satisfactory results and no disagreeable reactions whatsoever. These transfusions are graphically illustrated in Figure 2.

COMMENT

The advantages of a simple method of transfusing whole blood (and other fluids) to certain patients are obvious. Those patients who either because of their small size or because of having had repeated transfusions with resulting thrombosis of peripheral veins and the other local effects on the tissues of transfusions, particularly cutdowns, are very good candidates for this procedure. This

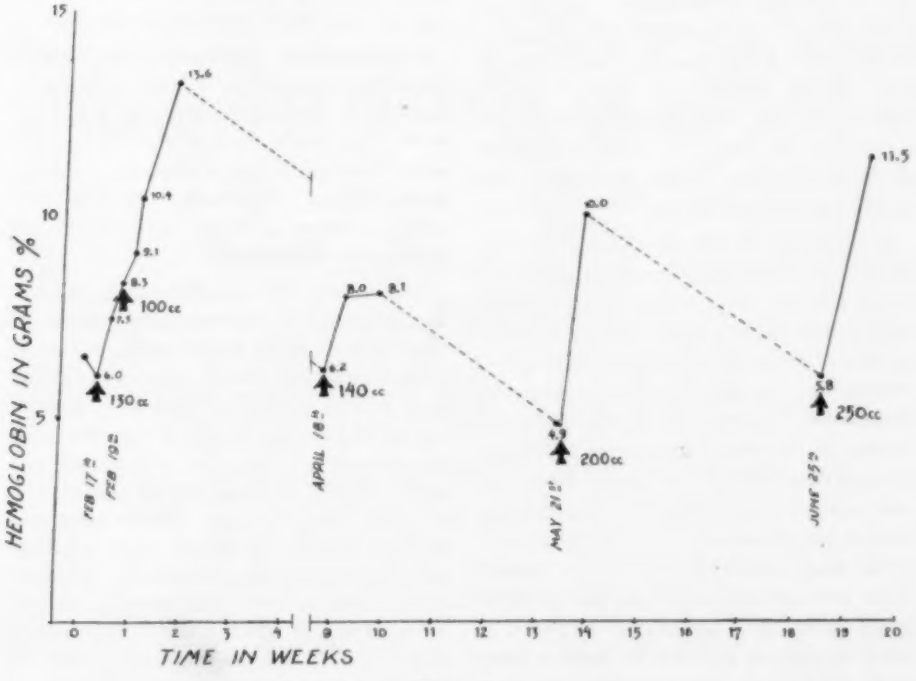

Figure 2

statement is true only if they do not need to have the blood volume restored within a matter of hours.

Several questions have arisen with regard to possible complications in connection with intraperitoneal transfusions.

1. *Formation of Adhesions.*—Although there is still considerable discussion as to whether or not blood in the peritoneal cavity is unduly irritating, the consensus is that fluid blood is not harmful. Most surgeons will remove only the clots of blood found in the peritoneal cavity following intraperitoneal hemorrhage in such conditions as ruptured ectopic pregnancy. In his discussion of this subject, Hedenstedt [10] described the case of a one-year-old girl with aplastic anemia who had had 10 intraperitoneal transfusions of 75 to 100 cc. each of heparinized whole blood prior to laparotomy for splenectomy. At operation the peritoneum was found to be "smooth and shining without any adhesions or other changes."

2. *Perforation of the Bowel.*—Experience indicates that the possibility of perforation of the bowel, with resulting peritonitis, is very remote. Porter and Carter [14] stated that "if a short bevel needle is used and reasonable care taken, it is almost impossible to do any damage to the intestine, a fact attested by many observers."

3. *Quantity of Blood.*—Because of the slower entrance of blood from the peritoneal cavity into the blood stream, it is doubtless safer to administer a larger amount by intraperitoneal transfusion than by intravenous transfusion. In his transfusions, however, Hedenstedt [10] gave 13% of the calculated normal blood volume because he noted that if more than 20% of the normal blood volume was given the abdomen was mildly distended for 24 hours. As noted by Ebert,[12] if the blood volume is normal and transfusions are used to correct anemia or hypoproteinemia, care should be exercised to avoid dangerous increase in blood volume, and under these circumstances the intravenous transfusion should not exceed 20% of the normal blood volume.

4. *Isotonicity.*—Since the danger of transient salt depletion and shock has been demonstrated by Darrow, using 5% dextrose solution intraperitoneally, it is unquestionably best to use as nearly an isotonic solution as possible. However, various investigators have used various preparations of red cells. Hahn and co-workers [9] used red cells separated by centrifuge and diluted with small amounts of saline. Hedenstedt [10] mentioned heparinized blood, and Siperstein [8] used citrated whole blood. Although we used citrated blood, there is no objection to the use of heparinized blood if this is thought more advantageous.

5. *Transfusion Reaction.*—Earlier workers questioned whether it was necessary to type and cross match blood for use in intraperitoneal transfusion. Clausen,[8] in 1938, demonstrated that the red cells enter the circulation intact, retaining their specific blood type, and stressed the importance of matching the donor blood with the recipient's.

6. *Discomfort.*—Apparently little, if any, discomfort is produced by the presence of blood in the peritoneal cavity, but it is noteworthy that four of Siperstein's [8] five patients showed low-grade febrile reactions following intraperitoneal transfusion. Hedenstedt [10] makes only the comment that some of the children "vomited a little."

It is theoretically possible that by the use of this procedure the hemoglobin values in cases of thalassemia major might be kept at a sufficiently high level to avoid some of the bone-marrow hyperplasia and bony deformity. Difficulties in intravenous administration are frequent in the practice of pediatrics, and intraperitoneal transfusion may prove to be of great value in those patients requiring repeated blood transfusions, such as those with thalassemia major, aplastic or hypoplastic anemia, nutritional anemias, or any other anemia in which it is not necessary to restore blood volume within a matter of hours.

SUMMARY AND CONCLUSIONS

A case of thalassemia major is presented in which intraperitoneal transfusions were used to produce a rise in the hemoglobin and hematocrit values.

The technique of intraperitoneal transfusions is summarized.

The advantages of this technique are mentioned and possible complications discussed.

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Splenectomy in Infancy and Childhood

The Question of Overwhelming Infection Following Operation

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The recent report by King and Shumacker,[1] reviewing the incidence of infections after splenectomy, suggests that this common operation is likely to be followed by meningitis or sepsis when performed in early infancy. Their series comprised approximately 100 cases, but the age limits were not stated. Of five infants splenectomized under 6 months of age, four contracted meningitis (two meningococcal, one Hemophilus influenzae, and one of undetermined type) from 5 to 31 months following splenectomy, while the fifth died of an illness strongly suggesting septicemia 1 month after splenectomy. These authors were able to find one similar case in a careful review of the literature, although they refer to a communication from Dr. Colin Ferguson to the effect that nine infants splenectomized at the Children's Medical Center under 6 months of age were alive and well one to six years later and that one child with a splenectomy at 7½ months of age died one year later of tracheobronchitis. Since so few data are available to confirm their conclusions that splenectomy in early infancy is followed by a high incidence of serious infection and death, we have been prompted to review the records of the years 1930-1954 at the Children's Medical Center, comprising some 200 splenectomies nearly all performed on children under 10 years of age. Essentially this is the group reviewed by Gross,[2] with some additions and omissions; cases were excluded in which the primary illness was a factor in susceptibility to infection (for example, leukemia) or in which some prior defect in the immune mechanism was known to exist, as in liver disease or nutritional failure.

Of the 62 splenectomies performed for congenital hemolytic anemia during the period reviewed, 10 were performed in children under 6 months of age. In a postoperative follow-up period of three years, none of these, with the exception of the case mentioned by Ferguson, has had any difficulty. We have not been able to locate the record of this single exception. Two infants were only 2 months of age, four were 3-5 months, and four were 6 months of age when splenectomy was carried out. This indicates that splenectomy under 6 months of age is not invariably followed by serious infection. Seven infants were between 6 months and 1 year of age at the time of splenectomy for congenital hemolytic anemia, and they have also had an uneventful course. Thus in 17 children under one year of age with splenectomy for congenital hemolytic anemia there were no apparent untoward sequelae.

Of the 45 remaining cases, only 1 so far as can be determined had any serious illness following splenectomy.

CASE 1.—A boy, born Dec. 24, 1934, was first admitted to the Children's Medical Center in 1937 because of pallor and weakness for two months and dysuria and red urine for one day. The family history was negative for congenital hemolytic anemia. Examination revealed slight lymphadenopathy and palpable liver and spleen. The red blood cell count was 900,000, hemoglobin less than 20%, white blood cell count 35,000, and reticulocytes 50%-75%. The urine contained hemoglobin and red blood cells.

Submitted for publication Oct. 31, 1955.

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Following transfusions, his hemoglobin value rose to 70%. Studies revealed slightly increased fragility of red cells.

In January, 1939, he was admitted again, with pneumonia and secondary anemia, and was treated with sulfapyridine with improvement. Other illnesses included measles at 2 months, bronchitis at 2 years, and varicella at 3 years, apparently uncomplicated. Because of the demonstration of increased fragility of the patient's red cells, a splenectomy was performed on Jan. 4, 1940, when he was 6 years of age. He apparently was well save for recurrent colds until April 10, 1940, when he developed progressive listlessness, fever, vomiting, and coma. Lumbar puncture yielded cloudy cerebrospinal fluid from which Type 19 pneumococci, Diplococcus pneumoniae were cultured; the child died 15 hours later despite therapy with sulfathiazole and specific rabbit antiserum. At autopsy, a diffuse pneumococcal (Type 19) meningitis was found, with mild otitis and pharyngitis. Blood culture was sterile, but there were signs of bronchial and interstitial pneumonia. In all organs there were striking accumulations of islands of reticuloendothelial cells or chronic inflammatory cells and marked hyperplasia and hypertrophy of lymph nodes, with occasional toxic reaction. The liver showed minimal hemosiderosis. A review of the spleen was unremarkable. No studies of γ-globulin were done on this child.

Of 23 children with splenectomy performed for idiopathic thrombopenic purpura, only one was under one year of age, and splenectomy in this case had been done at another hospital. One patient was one year old. With the exception of these two, all the other patients were over 3 years of age and had no difficulty following splenectomy.

Case 2.—A boy born Jan. 25, 1952, at the age of 6 days developed omphalitis, bloody stools, and severe impetigo following circumcision and required treatment with oxytetracycline and chloramphenicol (Chloromycetin). At the age of 6 months he had two hospital admissions for bronchopneumonia and anemia; a diagnosis of idiopathic thrombopenic purpura was made at this time. At the age of 6 months, splenectomy was performed because bleeding due to the thrombopenia was not controlled by cortisone or corticotropin (ACTH). The pathological report was consistent with idiopathic thrombopenic purpura. At 7 months of age he was hospitalized for one month because of pneumonia with dehydration and acidosis and at the age of 9 months with cough, fever, and otitis. His first admission to the Children's Medical Center was at 10 months of age because of severe rectal bleeding, which was treated with chemotherapy and platelet transfusions. At 14 months of age he was readmitted because of severe varicella and rectal bleeding.

At the age of 21 months he was admitted for Type 6 pneumococcal meningitis complicated by right hemiparesis and subdural effusion. At the age of 24 months he developed purulent arthritis of the left knee; no organism was isolated, however, but the patient responded to antibiotics. At this time studies of his γ-globulin level showed it to be normal. The child was Group O, with weak anti-A and no anti-B antibodies. At 24 months he developed right-sided convulsions and increased hemiparesis, probably related to the previous subdural effusions. At 25 months he developed croup, which was treated with chloramphenicol and was followed by thrush and Friedländer's pneumonia. It was noted that the platelet level, which had remained low despite the splenectomy, tended to rise with infections. At the age of 26 months he developed mumps and showed a rise in mumps hemagglutinin inhibition titer. In May, 1954, at 27 months of age, the patient developed Type 23 pneumococcal meningitis and bilateral pulmonary infiltration, thought possibly to be pulmonary moniliasis. Periodic γ-globulin injections were then given without apparent benefit. In November, 1954, bilateral burrholes were made, and the left subarachnoid space was found to be covered with cheese-like exudate. One month later he was admitted for pyogenic arthritis of the left knee and again for purulent otitis media. Because of suspected aqueductal block, a ventriculoperitoneal shunt was done. Arthritis of the right hip recurred in January, 1955; the hip was drained, but no organism was recovered, and he subsequently developed involvement of left hip, knees, and ankles and cellulitis of the feet. Repeated studies for agammaglobulinemia and dysglobulinosis were negative. In February, 1955, an adenoidectomy was performed. The child had another episode of bilateral parotitis at this time. His head had enlarged to 51 cm. On Feb. 18, 1955, he was admitted for rectal bleeding and treated with transfusions. X-ray studies showed no foci of osteomyelitis. He was admitted again on May 5, 1955, because of recurrent fever and joint symptoms, with tenderness and spasm over the right hip and bilateral otitis. Repeated studies have failed to establish any defect of the immune mechanism, nor have they shown any focus of infection. The only siblings of this child are half-siblings, and they are well.

Case 3.—A boy, born Aug. 5, 1951, was first admitted to the Children's Medical Center at 7 weeks of age because of hematemesis since 5 weeks of age. Studies revealed a platelet count of 72,000; stool guaiac test was positive and bleeding time and tourniquet test normal. Bone marrow was normal, with normal megakaryocytes. A diagnosis of thrombocytopenic purpura was made. He then had several subsequent admissions for parenteral diarrhea, with

bronchitis and upper respiratory infections. On his fifth admission, in August, 1952, at the age of one year, a splenectomy was done because the child was walking and the thrombopenia had persisted. He was given cortisone preoperatively, with only a minimal rise in platelets. Five months after splenectomy he was readmitted with Type 23 pneumococcal meningitis, with organisms recovered from blood, cerebrospinal fluid, nose, and throat. X-rays showed right upper-lobe pneumonia and left mastoiditis. The child made a good clinical recovery; subdural taps were negative, and he seemed to suffer no immediate ill effects. Two months later he was treated for multiple abcesses of the buttocks secondary to the penicillin injections from his previous admission. At the age of 27 months, he was readmitted with Type 9 pneumococcal meningitis and made a good recovery with therapy. Three weeks later he was admitted with fever, and a positive culture for Type 23 pneumococci in his cerebrospinal fluid was obtained, although no pus cells were found. This had occurred despite prophylaxis with heavy doses of oral penicillin. No treatment was given, and the child apparently recovered uneventfully. He was readmitted in May, 1954, because of fever, and though initial cerebrospinal fluid culture was negative, the child's blood culture and subsequent cerebrospinal fluid cultures grew out Type 14 pneumococci. He made a rapid recovery with penicillin and sulfadiazine. In June, 1954, he was readmitted because of a draining left ear. On this admission, a left mastoidectomy was done. At operation some old decalcified bone was found. Intensive studies failed to reveal any defect of γ-globulin, either quantitative or qualitative, although the child's response to mumps hemagglutinin antigen injection showed no rise in antibody titer. In addition, the patient's blood type was A and he had no anti-B hemagglutinins. Studies by Dr. David Gitlin revealed normal antibody formation against the various pneumococci responsible for his previous illnesses. On this admission he had a brief illness, consisting of migratory arthritis and fever diagnosed as a serum-sickness-like response to penicillin.

He then remained relatively well until March, 1955, when he was admitted with pneumonia and pyuria. Intravenous pyelograms were negative. He was last seen in April, 1955, with left otitis.

Of the remaining splenectomized patients, those with tumors, leukemia, portal hypertension, and storage diseases were excluded because of the nature of the primary disease. Of 18 patients ranging in age from 6 to 13 years with splenectomy for rupture of the spleen, none had any subsequent difficulty. Of four children with Cooley's anemia who had splenectomy, one case is reported in detail because of the seeming relation of splenectomy to sepsis.

Case 4.—This patient was born July 30, 1936, and was first admitted to the Children's Medical Center at 3 months of age because of pallor and lassitude. Physical examination showed the spleen to be at the iliac crest and the liver 4 fingerbreadths below the costal margin. Hemoglobin was 4.7 gm.; red blood cell count, 1,500,000, and there were 25,000 nucleated red blood cells per cubic millimeter. Fragility studies revealed increased resistance to hypotonic saline. A diagnosis of Cooley's anemia was made, and over the next two years the patient required 19 admissions and was given 38 transfusions, totaling 8500 cc. of blood.

Because of the diminishing interval between transfusions and the subsequent failure of nucleated red cells to appear in the peripheral blood, a splenectomy was performed when the patient was 25 months old. Following this, numerous nucleated cells made their appearance, and the interval between transfusions lengthened from three weeks to two to three months. Six months after splenectomy, the patient developed arthritis of the right knee, apparently suppurative, although no organism was cultured. He began to have numerous upper-respiratory infections, mostly streptococcal, adenitis, pyoderma, felons, and acute stomatitis. At the age of 3½ he was hospitalized at the Cleveland Clinic with pneumonia and ran a very stormy course. At 4½ years of age a tonsillectomy was done. In the period following splenectomy a total of 12,500 cc. of blood was given as periodic transfusions. X-rays later began to be consistent with Cooley's anemia, although the smears were never felt to be characteristic. At times oval cells were seen in the peripheral blood smears.

At the age of 5 5/12 years, he was admitted to the Children's Medical Center following 24 hours of fever, coma, and delirium. His hemoglobin was 42%, red cell blood count 2,200,000, white cell count 26,000, with 57% polymorphonuclear leucocytes, 33% lymphocytes, 4% eosinophiles cell, 1 monocyte, and 22,000 nucleated red blood cells. Spinal fluid was normal, but blood culture was positive for pneumococci eight hours later. At autopsy, no source of infection was found. The only pathologic changes were consistent with Cooley's anemia.

This boy's family history is interesting in that one sibling died at age 4 months of pneumonia and another at the age of 5 with the same illness. Both parents were of Syrian descent, and there was no other family history of Cooley's anemia. Two other siblings were alive and apparently in good health. No studies of γ-globulin or the immune mechanism were made in this patient.

COMMENT

In the present series of 107 splenectomies, 4 cases have been found with severe infections occurring after splenectomy. One patient had his splenectomy at 6 months, one at 1 year, one at 25 months, and one at 6 years. In all four cases, pneumococcal infections have played a major role. In the total series of 107 there were 17 patients splenectomized under one year of age.

There appears to be a correlation between the splenectomy in these cases and severe sepsis. This series does not bear out the relationship between age at splenectomy and severe sepsis described by King and Shumacher,[1] for two of our cases were older children. The hazard of splenectomy in early life in the present series is not as great as that recorded by these authors.

Gamma-globulin studies were carried out in two of our patients and failed to show any quantitative deficiency. In addition, unpublished observations by Dr. William Kiyasu have shown no drop in γ-globulin following splenectomy. We can speculate that splenectomy might induce qualitative changes in γ-globulin, as yet unmeasurable, but against this is the observation that γ-globulin failed to affect the course of one of the patients. It is also possible that the filter action of the spleen guards against bacteremia and septicemia, but data on this point are unavailable except in animal experiments. Rowley,[3] however, has reported that splenectomized humans fail to show as good an antigenic response to heterologous erythrocytes as do normal humans.

CONCLUSIONS

As with any *post hoc* study, only a limited and tentative conclusion is possible. From our series it would appear that splenectomy under one year of age is infrequently followed by severe infection. There does, however, appear to be a correlation between splenectomy and sepsis, apparently independent of age. The incidence of this correlation does not seem to be as great as would appear from the data of King and Shumacher,[1] and in our series amounts to about 5%. In two of our four cases severe infections such as pneumonia had preceded splenectomy. The nature of this proneness to sepsis or meningitis awaits further studies.

SUMMARY

Two hundred seven cases of splenectomy were reviewed for possible sequelae of severe infection. One hundred cases were excluded because of the underlying condition for which splenectomy was performed. Of the remaining 107 cases, 4 were apparently followed by severe infection. Two occurred in infants splenectomized under one year of age; the other two cases were in older children.

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The Prognostic Significance of Globulinuria in the Nephrotic Syndrome

An Electrophoretic Study of Urinary Proteins in the Nephrotic Syndrome and Acute Glomerulonephritis

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Globulin was detected in protein-containing urine for the first time in 1866, by Lehman.[1] From then on, several studies * have dealt with a possible relationship of globinuria to the outcome of renal diseases. Discrepancies in the results and conclusions obtained may be due to the use of older, inaccurate methods and to the fact that single or few examinations were done in individual cases. Further confusion also derived from the poorly defined classification of cases used for investigation, usually grouped under the term of "Bright's disease." We will confine our communication to 11 children who suffered from acute postinfectious hemorrhagic glomerulonephritis and to 32 children suffering from the nephrotic syndrome. According to a recently proposed classification,[10] children who had the nephrotic syndrome in its so-called "pure form" were not separated from children who at one time or another had the disease with hematuria, hypertension, or azotemia. According to this concept, the latter picture represents a stage of the same entity.

Received for publication Nov. 8, 1955.

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Supported by grants from the National Institutes of Health, U. S. Public Health Service (A-44), and the American Heart Association, Inc.

Dr. Louis Pillemer, Department of Pathology, and Dr. Carl H. Miller, Department of Biochemistry, Western Reserve University School of Medicine, gave assistance in this work.

* References 2-9.

MATERIAL AND METHODS

The nephrotic children were divided into three groups. A good prognosis seemed justified in 20 children, who remained free of hematuria, azotemia, and hypertension and in whom a good response to corticotropin (ACTH) or cortisone was regularly obtained. Three children given a guarded prognosis had episodes of gross hematuria, and at times had some azotemia and hypertension. The six patients in whom the outlook was thought to be grave died of renal failure during the two and one-half years of observation. Three further patients were investigated in a stage of arrested, not progressive, renal disease resulting from a previous nephrotic disorder. At the time of the study, they had some proteinuria, hypertension, and fluctuating moderate azotemia 5 to 10 years after their nephrotic syndrome had subsided. The final prognostic evaluation of these children rested on evidence obtained during the two and one-half years of observation. In 15 of the 32 nephrotic children studies of the urinary proteins were obtained 2 to 14 times at various intervals during the course of their disease. A total of 106 determinations were obtained in this group. In eight nephrotic children urine was obtained 14 times before and again three to four days after proteinuria had started to decrease owing to corticotropin or cortisone administration. In 11 patients with acute postinfectious hemorrhagic glomerulonephritis, urine was obtained for study within two weeks after onset of the disease. In all these patients urine was collected over a 24-hour period. It was kept without preservative in the icebox during that time. Total urinary protein determinations were carried out according to Shevky and Stafford.[11] The electrophoretic study of urinary proteins was carried out with the conventional Tiselius method. The determinations were run for three hours with 15 ma. at a temperature of 1.5 C. Barbital (Veronal) buffer

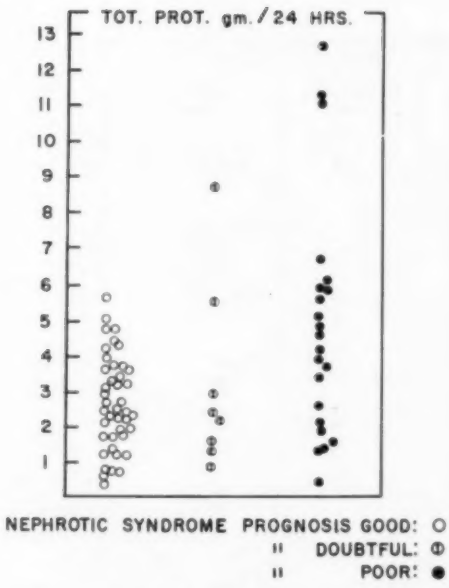

Fig. 1.—Quantitative determinations of protein excretion (grams per 24 hours) in the urine of 32 nephrotic children. The values are grouped according to prognostic evaluation.

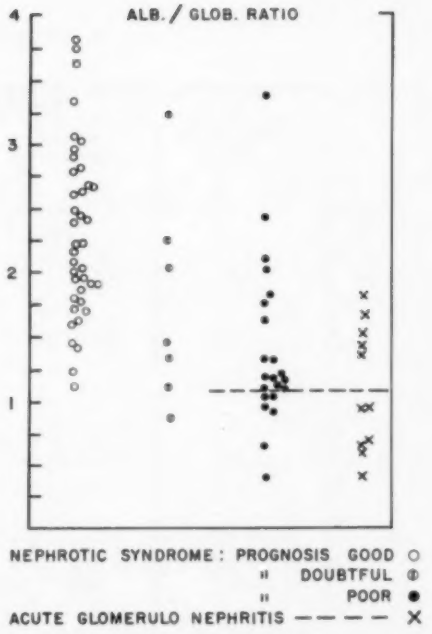

Fig. 3.—Albumin globulin ratio in the urine of 32 nephrotic patients and 11 children with acute glomerulonephritis. The values for the nephrotic patients are grouped according to prognostic evaluation.

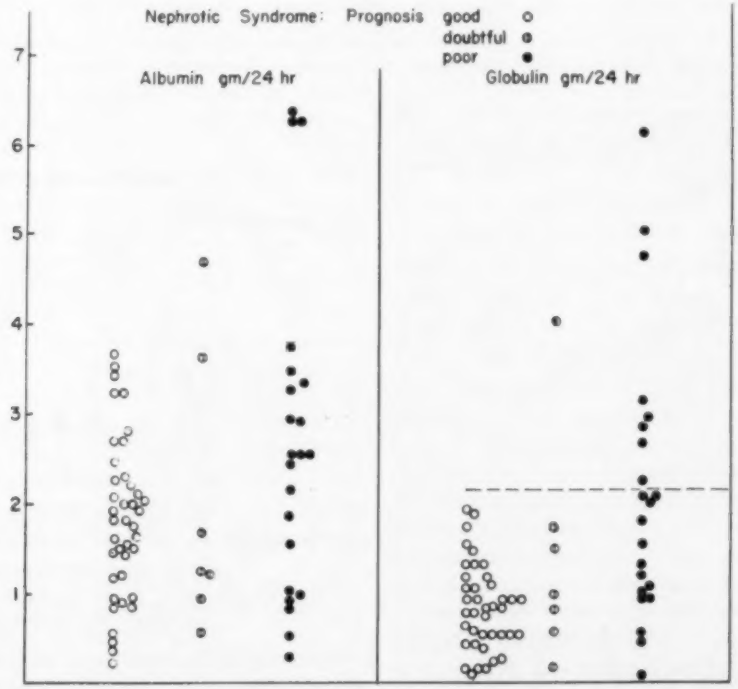

Fig. 2.—Quantitative determinations of albumin and globulin excretion (grams per 24 hours) in the urine of 32 nephrotic children. Values are grouped according to prognostic evaluation.

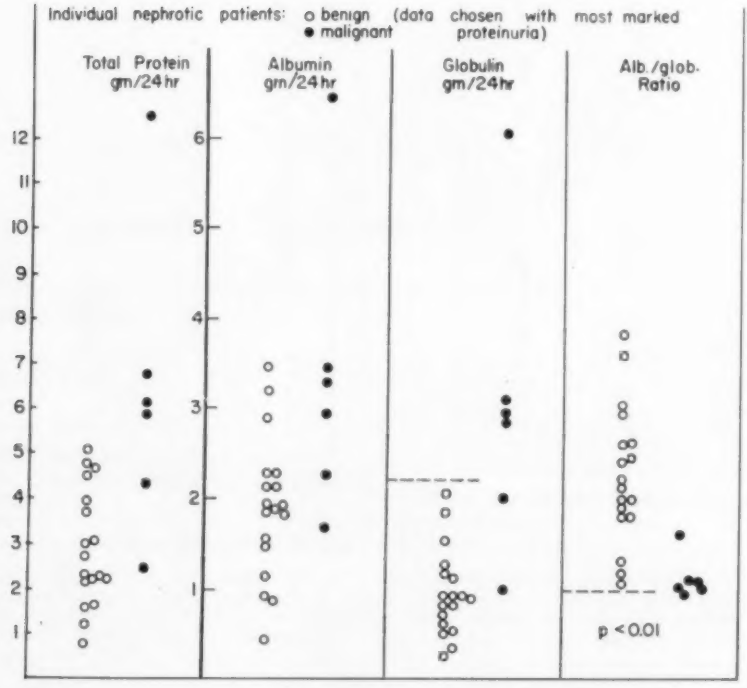

Fig. 4.—Data obtained in 24 individual nephrotic patients. The values chosen from repeated determinations in the same patient correspond to the most marked degree of proteinuria.

(pH 8.5 and ionic strength 0.1) was used. The urinary protein concentration was adjusted by dilution or concentration to 1.5% before determinations were carried out.

RESULTS

The amounts of proteins lost in the urine in 24-hour periods in 32 nephrotic children are shown in Figure 1. The 72 determinations were obtained before treatment with corticotropin or cortisone was started at various times during the course of the disease. Even though there does not seem to be a significant difference in the intensity of proteinuria between the three prognostically different groups, it is worth noting that none of the patients with "benign" nephrosis excreted (in 42 determinations) more than 5.8 gm. of protein per day, while eight urine samples (in a series of 30 determinations) obtained from nine of the children who at some time had hematuria, hypertension, and azotemia,

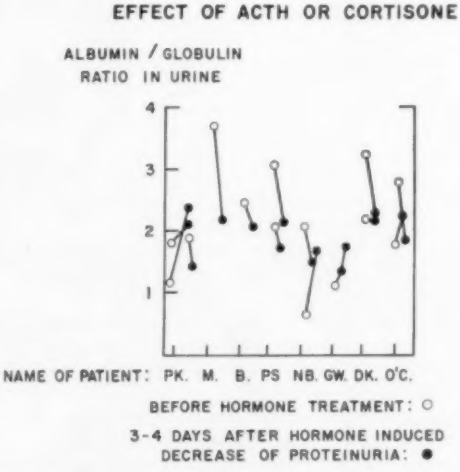

Fig. 5.—Effect of corticotropin or cortisone on the albumin-globulin ratio in the urine of eight nephrotic children.

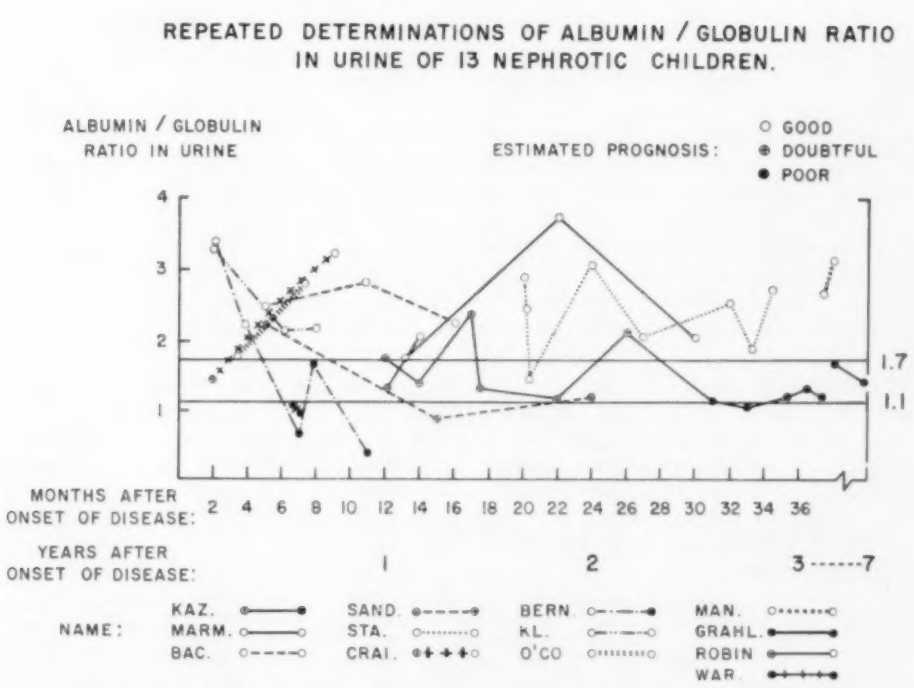

Fig. 6.—Albumin-globulin ratio in the urine of 13 nephrotic children obtained repeatedly in the same patient during the course of the disease.

showed 6 to 13 gm. of protein per 24 hours.† Figure 2 shows the electrophoretic determination of albumin and globulin excreted per day in these specimens. Among the three prognostically different groups there is no significant difference in the amounts of albumin excreted per day. However, none of the 40 determinations obtained in the 20 children with so-called "pure lipid nephrosis" yielded globulin values in excess of 2.0 gm. per day, whereas 11 of 29 urine specimens obtained from 9 nephrotic children who had had hematuria, hypertension, or azotemia yielded between 2.1 and 6.15 gm.‡ In terms of the urinary albumin/globulin ratio (A/G ratio) (Fig. 3), none of the patients with benign nephrosis had a value lower than 1.1, whereas 7 of 29 urine specimens obtained from the nine patients that did or still may develop renal failure yielded values between 0.38 and 1.1.§ It should be pointed out that the A/G ratio in the urine of 11 cases of acute glomerulonephritis was six times less than 1.0 and five times between 1.3 to 1.85.

Considering that the data noted in nephrotic children were frequently obtained repeatedly in the same patient during various phases of the disease, a statistical evaluation of the results should be based on single representative data obtained from individual patients.‖ For this purpose values were chosen from repeated determinations obtained in the same patient that corresponded to the most marked degree of proteinuria quantita-

† Owing to the inequality of the studies performed in the two groups, these data do not lend themselves to statistical evaluation.

‡ Owing to the inequality of the studies performed in the two groups, these data do not lend themselves to statistical evaluation.

§ Owing to the inequality of the studies performed in the two groups, these data do not lend themselves to statistical evaluation.

‖ Dr. George F. Badger, Professor of Biostatistics, Western Reserve University School of Medicine, gave help and guidance in this evaluation.

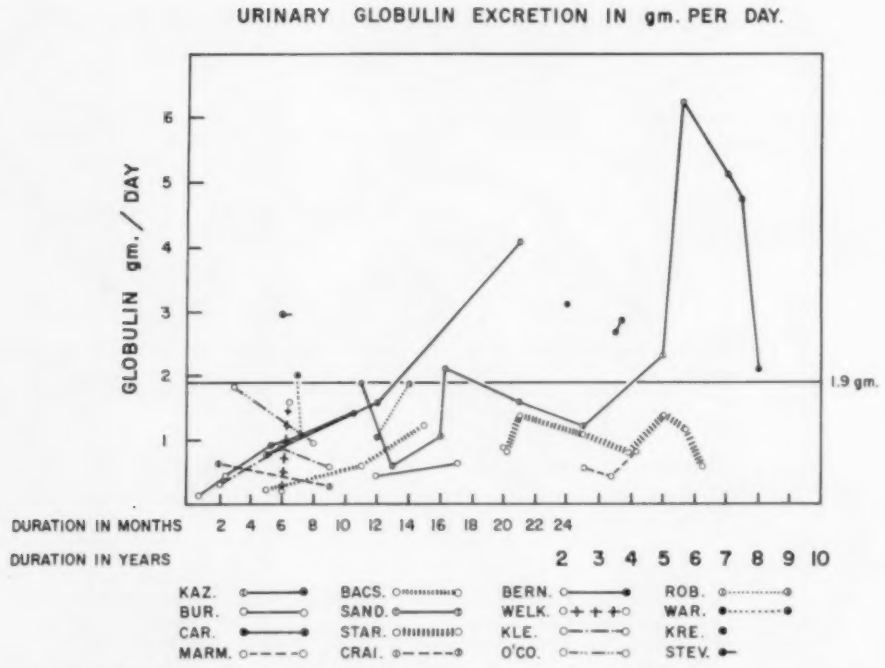

Fig. 7.—Excretion of globulin (grams per day) in the urine of 16 nephrotic children obtained repeatedly in the same patient during the course of the disease.

tively determined by the urinary excretion of total proteins per 24 hours. Figure 4 shows these data. It can be seen that under these conditions proteinuria was severer in nephrotic children in whom progressive renal disease had developed ($P<0.01$) and that this was due chiefly to an increased excretion of globulins. The average A/G ratios were, correspondingly, 2.25 for the prognostically benign group and 1.06 for those in whom the disease took a progressive course. The difference noted is significant in that the P value was smaller than 0.01.

It has been shown that hormone-induced diuresis is regularly preceded by a decrease of proteinuria.[12] It thus seemed of interest to investigate whether corticotropin or cortisone alters the excretion of albumin or globulin predilectively. In eight nephrotic patients electrophoretic studies of the urine were obtained 14 times before hormone treatment was started and were repeated three to four days after proteinuria had started to decrease. Figure 5 shows that no regular effect of these agents on the urinary A/G ratio was noted at a time when total protein excretion had already been decreased.

Figure 6 represents values for the A/G ratio, and Figure 7, the amounts of globulin excreted in the urine in grams per 24 hours obtained in 50 repeated examinations during the course of the disease in 16 nephrotic patients. None of the nephrotic children in whom the prognosis seemed favorable had a ratio of less than 1.4. Only patients with definite evidence of renal failure or children with gross hematuria, hypertension, fluctuating azotemia, and unsatisfactory response to hormone treatment had values below 1.4. It should be noted that in some patients the ratio reversed during the course of the disease, from high to low values and vice versa (Fig. 6; Bern., Sand., Crai., Robin). The ratio is thus not fixed and not necessarily predetermined at the onset of the disease. In Figure 7 it can be seen that amounts in

excess of 1.9 gm. of globulin were excreted only by nephrotic children with poor or doubtful prognosis. It has to be emphasized again that this was not predetermined in early phases of the disease and that these data, naturally, depended to a great extent on the amount of urine excreted per 24 hours.

COMMENT

The foregoing studies reveal that an increased amount of globulin is frequently excreted in the urine of nephrotic children in whom the renal lesion progresses to glomerular fibrosis and atrophy. A urinary A/G ratio less than 1.1 (or a urinary excretion of globulins in excess of 45% of the total proteins) is of poor prognostic implication. Because the amounts of urinary globulins excreted in 24-hour periods are dependent on urinary output, which in turn depends in part on the tendency to develop edema and ascites, these latter figures are less dependable. Still, an excretion of more than 2 gm. of globulin within 24 hours has only been noted in children who ultimately died in renal failure. It is to be noted that the A/G ratio in the urine of children with acute postinfectious hemorrhagic glomerulonephritis is around 1.1. If Blackman's [18] contention is correct, that a high globulin concentration in the glomerular space promotes crescent and adhesion formation, the lower total protein concentration and the usually short duration of proteinuria in glomerulonephritis would provide an explanation for a different prognostic implication of a similarly low A/G ratio in acute glomerulonephritis. The prognostic value of an A/G ratio of less than 1.1 or of an excretion of more than 2.0 gm. per day of globulins in the urine of nephrotic children is limited in that this finding has not necessarily been obtained in early phases of the disease. A further limitation has to be recognized in the possible reversibility of the A/G ratio during the course of the renal disease (Fig. 6; Crai., Robin). Yet in four instances (Fig. 6; Sand., Bern., War., and Fig. 7; Stev.) this test indicated a malignant course at a time when other symptoms (hematuria, azotemia, creatinine retention, hypertension, hyperphosphatemia, or hyperpotassemia) did not justify a similarly grave prognosis. The only other indication of a poor outlook available at the time in these four patients was the unsatisfactory response to hormone therapy (incomplete diuresis in four, and convulsions not due to hypocalcemia in one of these children).[19] It is of interest that the effect of corticotropin or cortisone on proteinuria in the nephrotic syndrome is not associated with a selective effect on the excretion of albumin or globulin. If one accepts the view [18] that globulins promote adhesion and crescent formation in the glomeruli, the hormone-induced decrease of proteinuria, which concomitantly decreases the concentration of globulins in the glomerular space, could possibly explain the favorable effect that the planned long-termed administration of these hormones seems to have on the course of the disease.[18] This assumption is, however, hypothetical.

SUMMARY

Urinary proteins were studied by electrophoresis (Tiselius method) in 11 children with acute glomerulonephritis and 32 children suffering from the nephrotic syndrome (109 determinations).

Twenty-four-hour losses of urinary protein in excess of 6 gm., losses of globulin in excess of 2.1 gm., and an A/G ratio in the urine of less than 1.1 were only noted in nephrotic children whose disease progressed to renal failure.

When corticotropin (ACTH) or cortisone diminish proteinuria, the urinary A/G ratio is not specifically affected.

The A/G ratio in the urine of children with acute glomerulonephritis varied between 0.3 and 1.85. Because proteinuria is less marked and lasts less long, the magnitude of urinary globulin excretion is, however, much smaller than in the nephrotic patient.

In spite of certain limitations, the extent of globulinuria and the determination of the A/G ratio in the urine proved to be of prognostic value in four instances in which definite evidence of ensuing renal failure was not yet available.

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Peritoneal Granuloma Due to Enterobius Vermicularis

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The general review article by Symmers [1] leaves little to be added to the description of the pathology of extraintestinal granulomas due to Enterobius vermicularis. The purpose of the present report is simply to describe a case of Enterobius granuloma in the pelvic peritoneum of a 16-month-old white girl, apparently the youngest patient so far reported in whom such lesion has been found.

Symmers reviewed the world literature and found 16 cases of pelvic peritoneal lesions containing Enterobius or its ova, and he added two such cases of his own as well as a third case of a granuloma in a ureter. Only 2 of these 18 peritoneal granulomas were of clinical significance, the remainder being incidental necropsy or surgical findings.

Since publication of Symmers article, there have been other case reports of granulomas due to Enterobius in the female genital tract and the abdominal cavity.*

Fatheree and co-workers [2] reported a case of abscess in the posterior wall of a uterus removed because of low back pain and retroversion in a 26-year-old woman. The abscess contained eggs and an adult Enterobius and was an incidental finding considered by the pathologist as not responsible for the clinical signs and symptoms. The peripheral blood showed 14% eosinophiles.

Gill and Smith [3] reported two cases of typical Enterobius granulomas of the ovary, neither being of surgical significance. In one case a woman aged 37 was operated on in early gestation because of severe edema and hypertension. There was a 0.5 cm. nodule beneath the serosa of one ovary which was a typical granuloma containing Enterobius ova. The second case was in a 29-year-old woman undergoing elective surgery. A 1.2x-0.6x0.8 cm. polypoid mass was found on one ovary which contained both ova and adult worms. The peripheral blood picture was not mentioned in either case.

Nairn and Duguid [5] found an Oxyuris granuloma in endometrial tissue removed from a woman of 45 years during routine curettement several days prior to hysterectomy for prolapse of the uterus. No other signs of Oxyuris infestation were found in the uterus when subsequently examined.

The patient related that she "suffered from worms on and off for 30 years" but had not sought treatment. She had last noticed worms in her stools about two months prior to her hospital admission. The authors state that pruritus and menorrhagia of six months' duration were the only symptoms present which might have been related to the worm infestation.

Heim [4] discovered several small, pea-sized nodules just above the right sacrouterine ligament in a woman of 30 years. Previous pelvic examination had revealed a nodular enlarged uterus and the firm nodules on the right sacrouterine ligament. The peripheral blood cell count showed 5% eosinophiles. A diagnosis of endometriosis was made, and exploratory operation was done because of a desire of the patient to have children.

The pathologist's report was "granuloma with masses of worms in the interior." After

Submitted for publication Nov. 15, 1955.

From the Laboratory of Surgical Pathology, St. Elizabeth's Hospital.

* References 2-5.

the operation pinworms were found in the patient's stools.

Heim believes that the worms entered the peritoneal cavity through the genital tract. He did not think the nodules were responsible for any clinical symptoms or for the thin adhesions present in the pelvis which were found at operation.

In his conclusions Symmers says: "Oxyuris only exceptionally causes pathologic changes in the tissues, its pathogenicity in this respect being trivial; nevertheless, it can, on rare occasions, alone produce such changes, and a more definite stand must be taken on this subject than that of such authors as Lane and Napier."

Lane [6] states: "The worm rarely does conspicuous harm, but careful examinations have shown the hosts' health to be subnormal," and "Further study will no doubt take up the question of the extent to which treatment has rid a host of other infections which too may have injured health."

Napier [7] believes no very convincing evidence has been presented that Enterobius vermicularis may cause lesions in the intestinal tract. He is not impressed with evidence of acute or subacute appendicitis due to the worm, or even of its predilection for that organ. Napier concludes: "There is a little evidence that in heavy infections in ill-nourished children some invasion of the mucosa may take place with resultant diarrhoeal and other disturbances but with this possible exception it seems very doubtful if any of the varied symptomatology that is popularly attributed to this worm is really caused by it."

The case reported herein clearly demonstrates that E. vermicularis can produce clinically significant pathology and symptoms that may be confusing to the physician. Inasmuch as the widespread prevalence of threadworm infestation in children has been demonstrated repeatedly, the clinician should consider the possibility of an Enterobius granuloma in the differential diagnosis of a pelvic mass in children.

There are three features of the present case which make it worth recording. These features are (1) the large pelvic granuloma which produced the symptoms leading to surgical intervention, (2) the demonstration of E. vermicularis ova and fragment of adult worm in the granuloma, and (3) the age of the patient, the youngest so far recorded.

REPORT OF A CASE

A 16-month-old white girl was admitted to St. Elizabeth's Hospital on May 9, 1955. The chief complaint, as given by the mother, was constipation, with the stools much smaller in circumference than usual.

The child had been healthy and well from birth until April 18, 1955. At that time the patient developed fever (temperature 103 F), appeared ill, and had a dry, hacking, paroxysmal cough. The mother noted that the child appeared to be "sore" all over and cried if touched or picked up. She was treated by the family physician for bronchitis; penicillin and one of the "mycins" were given. Within 48-72 hours the cough had subsided, but nausea, vomiting, and diarrhea appeared. This was attributed to the antibiotics, which were stopped.

Within another 24-48 hours, the nausea, vomiting, and diarrhea cleared up, and the child felt much better, but the mother began to notice the "pencil" stools. The child was examined by a pediatrician, and a rectal mass was felt; so she was referred in for study.

On admission the patient was noted to be a pale, well-nourished, 16-month-old white girl, who did not appear ill. She weighed 22 lb. and seemed to be alert and oriented. Physical examination was within normal limits, except that on rectal examination a large, firm fixed mass filled the pelvis. This mass could not be felt abdominally. No lymphadenopathy was present.

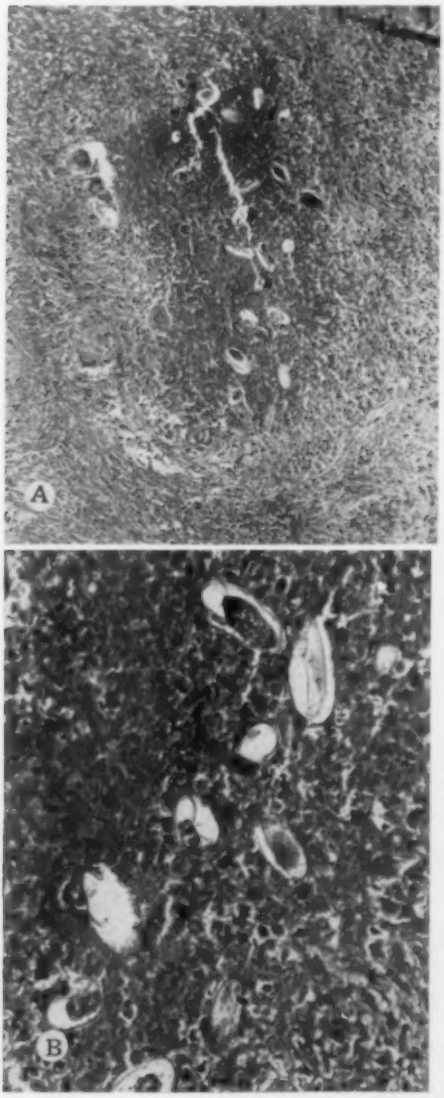
Blood tests showed 11 gm. (72%) of hemoglobin, with 4,450,000 RBC. WBC numbered 12,750, with polymorphonuclear leucocytes 36%, lymphocytes 52%, and eosinophiles 12%. Rectal temperatures ranged between 99 and 100.2 F.

On May 10, cystoscopic examination was carried out, and it was felt that an extrinsic lesion was compressing the bladder forward. On May 11, 1955, laparotomy was done, and the pelvis was found to be distorted by a retroperitoneal mass, which felt like a large matted group of lymph nodes, filled the peritoneum beneath the cul-de-sac, and extended up along the internal iliac vessels. In addition, large smooth shotty lymph nodes (the size of lima beans) were present up the aortic chain. The sigmoid colon was adherent into the cul-de-sac by what was thought to be malignancy or chronic inflammatory tissue. The sigmoid was freed, and this tissue removed for biopsy. The remaining intra-abdominal

organs were not unusual in size, shape, appearance, or consistency.

The postoperative course was uneventful, with rectal temperatures ranging from 99-101 F. X-ray of the chest was within normal limits, except for some mediastinal shift to the left, cause not apparent.

Fig. 1.—*A*, photomicrograph showing ova of Enterobius vermicularis in foreign-body granuloma; reduced approximately ¼ from mag. × 100. *B*, higher power view of ova; reduced approximately ¼ from mag. × 400.



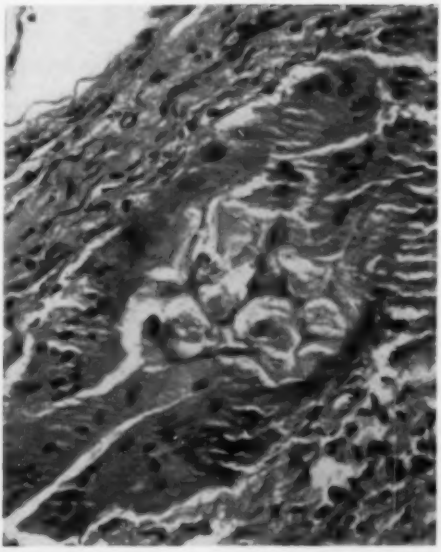


Fig. 2.—Photomicrograph showing fragment of body of adult worm in foreign-body giant cell; reduced approximately ¼ from mag. × 400.

A P. P. D. skin test (intermediate strength) was negative.

Pathological examination of the gross structure revealed a 0.5 cm. wedge-shaped piece of firm, gray tissue. Microscopic examination of sections showed fibrous connective tissue tending to form a capsule around a small central zone of necrotic tissue in which were numerous oval eggs of E. vermicularis and several foreign-body giant cells (Fig. 1*A*). There was a dense, diffuse infiltration of chronic inflammatory cells, most of which were eosinophiles. Folded larvae were present in some ova, although most ova contained only the characteristic basophilic chromatin aggregates of the later stages of segmentation (Fig. 1*B*).

Near the edge of the specimen, at a deeper level in the paraffin block, there was found a fragment of the body of an adult worm completely surrounded by foreign-body giant cells (Fig. 2). Remnants of the shell of degenerated ova could be seen in some of the sections.

The importance of examining several sections in a given block of tissue, as emphasized by Symmers, was well demonstrated in this case. The fragments of the adult were found in deeper levels of the specimen, where only occasional ova were found.

COMMENT

All reported cases of pelvic peritoneal granulomas have been in female patients. Adult female threadworms or ova have been

found in vagina, cervix, uterus, and Fallopian tubes. Passage of adult threadworms through the normal intestinal wall has never been demonstrated. The genital tract is considered to be the route by which E. vermicularis reaches the peritoneal cavity. There is nothing in the present case to implicate any other mode of entry.

One postulation to explain all the signs and symptoms of this case would be that the female worm or worms entered the peritoneal cavity through the genital tract and incited the granuloma. Extension of the resulting lymphadenitis upward via the aortic (demonstrated at surgery) and posterior mediastinal lymphatic chain could have been responsible for the fever and cough noted three weeks prior to hospitalization. The lymphadenitis subsided under antibiotic therapy, but the pelvic mass continued to increase in size to produce the "pencil-like" stools by pressure upon the rectosigmoid area.

Three months after the operation the patient was reported to be free of symptoms since release from the hospital, with normal appetite and weight increase.†

†Kiser, J. B.: Personal communication to the author.

SUMMARY

A granuloma of the pelvic peritoneum due to E. vermicularis is reported. This is the 20th such lesion reported in the literature and only the 3d one to directly cause symptoms leading to surgical intervention. The 16-month-old girl is the youngest in whom such lesion has been reported.

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Asterol

Further Search for Neurological Disturbances

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In a preliminary report [1] we described our findings in 39 children who had received topical applications of Asterol (2-dimethylamino-6 [β-diethylaminoethoxy]-benzothiazole) dihydrochloride for the treatment of tinea capitis. Pertinent to this subject was the high incidence (38%) of abnormalities in the pretreatment EEG's of these patients. Two children developed hallucinations during therapy, and three others showed electroencephalographic changes only. Reapplication of Asterol in polyethylene glycol (Carbowax) to four of these patients for prolonged periods of time failed to reproduce these findings. We have extended our search for neurologic disturbances, and it is the purpose of the present communication to describe and review our experience with a total of 151 children, who were observed for signs of neurotoxicity associated with the administration of Asterol.

All of the patients in this study were obtained from the tinea-capitis clinic at this hospital. The patients were divided into two groups as follows: The first consisted of 77 cases (of which 39 were previously reported) treated with 5% Asterol dihydrochloride in a polyethylene glycol base ointment. Since we considered the possibility that neurotoxicity might be facilitated by the child's sucking his fingers after rubbing his hand on his head or by sucking his Asterol-impregnated skull cap, we sought to decrease the drug residue on the scalp by using 5% Asterol dihydrochloride in a vanishing cream base ointment in the second group of 74 children.

An initial electroencephalographic and neurologic examination was made prior to treatment in all of the children who received Asterol in polyethylene glycol and in 23 of those who were treated with Asterol in vanishing cream. The neurologic and electroencephalographic studies were repeated monthly or at shorter intervals until treatment for tinea capitis was concluded. For EEG's eight scalp electrodes were used routinely with interconnected ear grounds. Bipolar combinations between neighboring electrodes were recorded upon an eight-channel Grass electroencephalograph, using a sensitivity of 6 to 8 mm. per 50μv. Each recording lasted 24 minutes, and children old enough to understand the request were hyperventilated vigorously for 2 minutes, followed by a 2-minute posthyperventilation record. In classifying the records we took into account maturation factors and allowed a significant latitude in interpreting the amount of slow activity which might appear in children of the same chronological age. No record was classified as slow that we did not believe to contain an excess after variability had been taken into account.

After the initial neurologic examination and EEG, the parents were instructed to apply 5% Asterol ointment morning and night, using 2 ounces (60 cc.) weekly. The scalp was shaved or clipped closely once weekly and shampooed every second day. No instructions were given concerning the use or care of skull caps. Whereas all of the patients treated with Asterol in polyethylene glycol had serial EEG's taken, this

Submitted for publication Nov. 28, 1955.

Department of Pediatrics and Neuropsychiatry, Washington University School of Medicine, and the St. Louis Children's Hospital. Supported in part by a grant from Hoffmann-La Roche, Inc.

applied only to 23 of the 74 patients receiving Asterol in vanishing cream. Comparisons between the two groups therefore had to be made on the basis of signs of clinical neurotoxicity.

The age range in these children was 9 months to 14 years, and the distribution was comparable in the two groups. The total duration of treatment with Asterol in polyethylene glycol was 916 weeks (77 cases), with an average of 11.9 weeks. Asterol in vanishing cream was used for a total of 903.5 weeks (74 cases), with an average of 12.2 weeks.

In addition to the five cases reported previously,[1] there was one child who developed hallucinations after five weeks' treatment with Asterol in polyethylene glycol. The EEG obtained prior to treatment was interpreted as borderline slow dysrhythmia for age. The EEG at the time of the hallucinations had significantly higher voltage than previously, and there were several runs of spike-like processes. The child made an uneventful recovery and was discharged after three days' hospitalization. Treatment with Asterol was reinstituted a week later and continued for seven weeks, during which time 10 ounces (300 cc.) of Asterol was used. Repeated EEG's and clinical examinations revealed no significant change from the pretreatment findings, and there was no further evidence of toxicity.

There were no clinical signs of toxicity in the children who were treated with Asterol in vanishing cream. Of those on whom serial EEG's were made, one showed slow spikes in a sleep EEG after 19 weeks of therapy, and two others had inconstant changes in the EEG patterns. In these three cases, all of the alterations noted were accountable on the basis of day-to-day variations in records of their age range. In no instance did new frequencies appear in these records.

One 7-year-old boy, who had a history of a febrile convulsion at the age of 4 years, failed to return after six weeks of therapy, at which time he was asymptomatic. Another patient, aged 8 years, had a sibling subject to febrile seizures; this child received 16 weeks of therapy without ill effect.

Although there is a statement on the package of Asterol warning against the use of the drug in children under 2 years of age, we had occasion to see a 9-month-old white girl who was treated with Asterol in vanishing cream from Nov. 9, 1954, to Jan. 18, 1955. The tinea capitis was cured without any clinical signs of neurotoxicity.

In our over-all experience with both forms of Asterol, we have observed six cases where there were EEG changes, clinical neurotoxicity, or both, concurrent with the administration of Asterol in polyethylene glycol .This number includes all episodes, regardless of factors other than Asterol which might have influenced or provoked the reaction. The duration of treatment with Asterol before the reaction ranged from 12 to 60 days, with an average of 33 days. Five of the six cases were again treated with Asterol; the duration of this second exposure ranged from 35 to 75 days, with an average of 54.4 days. In spite of the fact that in every patient the duration of the second exposure was greater than that of the first course of the drug, there was not a single instance of toxicity as revealed by the clinical history, by the EEG, or neurologic examination.

COMMENT

One patient who was being treated with Asterol in polyethylene glycol had EEG changes without clinical symptoms after sucking his Asterol-impregnated skull cap. This led to consideration of the possibility that it was the oral ingestion of the drug which provoked neurologic reactions. Since thumb sucking is common in young children, it was not unreasonable to assume that a drug applied to the scalp might find its way to the child's fingers and thence to the mouth. The vanishing cream base was consequently used in an effort to reduce the amount of residual ointment on the scalp. The hypothesis that oral ingestion was responsible for toxicity was supported by the absence of any signs of clinical neurotoxicity in the 74 children who were treated with Asterol

in vanishing cream compared with 3 patients who developed hallucinations in the Asterol in polyethylene glycol series.

The reaction apparently associated with the administration of Asterol in polyethylene glycol evades good definition. Be it sensitivity, allergy, idiosyncrasy, or toxicity, the most significant fact is the failure of the renewed application of the drug over a long period of time to provoke the same evidence of toxicity that appeared during the first course of therapy. Indeed, the literature contains but one report where the second application of the drug produced renewed signs of toxicity.[2]

Our experience shows that it is necessary to obtain pretreatment EEG's and neurological data if any valid interpretation is to be made of reactions during therapy. This is particularly important in children, as 38% of the initial EEG records showed activity outside the normal range for age.

SUMMARY

Seventy-seven children were treated for tinea capitis with 5% Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) dihydrochloride in a polyethylene glycol (Carbowax) base ointment. Pretreatment and serial EEG's and neurologic examinations were obtained.

Seventy-four children with tinea capitis were treated with 5% Asterol dihydrochloride in a vanishing cream base ointment. Twenty-three had pretreatment and serial EEG's and neurologic examinations. Fifty-one were observed only for clinical evidence of toxicity.

There was no evidence of toxicity in the children treated with Asterol in vanishing cream.

The reactions which occurred during the first course of therapy with Asterol in polyethylene glycol could not be provoked by a second extended course with the identical preparation.

The hypothesis is made that reactions following the administration of Asterol may be due to oral ingestion rather than cutaneous absorption.

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Studies in Cystic Fibrosis

Determination of Plasma Proline Following Protein Feeding as a Diagnostic Test for Pancreatic Insufficiency

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An earlier study [1] suggested a diagnostic procedure for pancreatic insufficiency associated with cystic fibrosis of the pancreas based upon the determination of plasma glycine following gelatin feeding. West, Wilson, and Eyles [2] had shown that a much smaller rise in blood amino nitrogen occurs in children with cystic fibrosis than in normal children after a test meal of casein. Christensen and Shwachman [1] confirmed the suggestion that gelatin might serve as a more suitable test protein and were able to avoid (1) the technical difficulties involved in the manometric ninhydrin determination of amino nitrogen or (2) the use of unsatisfactory colorimetric amino nitrogen methods by determining the change in plasma glycine concentration by a suitable method.[3] The selection of a single amino acid for estimation was based on the fact that gelatin contains somewhat more than 25% of glycine. The method is, however, not suitable for diagnostic purposes following a casein meal, since this protein contains but a small amount (2.7%) of glycine. It is frequently desirable to be able to determine the retardation of the absorption into the blood stream of amino acids derived from protein ingestion due to the failure of pancreatic proteinases in infants where milk or casein constitutes a more convenient test meal and where an amount of gelatin adequate for the test is not so easily administered.

With the development of a simple and convenient method for the determination of proline and hydroxyproline by one of us,[4] it has now become possible to modify the original diagnostic procedure to encompass both types of test meal since in addition to its high content of aminoacetic acid, gelatin contains 17%-19% proline and 14% hydroxyproline. Casein is also relatively rich in proline, containing slightly in excess of 10%. Furthermore, the determination of proline by the newly proposed method is considerably less complex than the determination of glycine. The sensitivity of the proline determination is such that fasting levels may be determined on 1 ml. of plasma or serum.

EXPERIMENTAL DATA

The test was carried out on healthy infants and children and on patients with cystic fibrosis of the pancreas having complete pancreatic insufficiency as determined by duodenal assay for the digestive enzymes, trypsin, amylase, and lipase. The procedure is to feed, 8 to 12 hours after the last meal, 1.5 gm. of an aqueous solution of the protein per kilogram of body weight. The solution as given to the patient is approximately 15% protein. In some instances the patients with pancreatic insufficiency were given papain,[5] a proteolytic enzyme derived from the tropical papaya plant, along with the protein test meal, in order to determine whether the administration of proteolytic enzymes will correct the proteolytic defect. Venous blood is collected just before the feeding and 120 or 150 min-

Submitted for publication Dec. 20, 1955.

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This study was supported in part by a Grant from the Sterling-Winthrop Research Institute.

utes later. The plasma is separated and is ready to be deproteinized with uranium acetate. The "apparent proline" * is then determined by the following procedure.

METHODS

Reagents.—1. Nitroprusside-aldehyde reagent: Dissolve 2 gm. of sodium nitroprusside ($Na_2Fe(CN)_5NO.2H_2O$) in about 50 ml. of cold distilled water. Add 20 ml. of cold highest quality acetaldehyde to the cold solution. Make up to 100 ml. with cold distilled water. Carefully adjust to pH 7.0, using solid sodium bicarbonate and an external indicator paper. When the reagent is not in use keep in the refrigerator. Reproducible results have been obtained with reagent that is several weeks old, but the stability varies from lot to lot. It is preferable to make up the reagent fresh, and it should always be checked against known standards at the time determinations are made.

2. 4% sodium carbonate solution.

3. 0.8% uranium acetate solution.

Standard Curve.—To quantities of proline varying from 0.1 to 1.0 μM. (11.5γ-115γ) in 1 ml. of 0.3% salt † add 0.25 ml. of nitroprusside-aldehyde reagent and 0.5 ml. of water. Allow the mixture to stand for two minutes and add 0.25 ml. of sodium carbonate solution. After one to three minutes read the color in a photocolorimeter, using a 600 mμ filter. The instrument is previously set to zero optical density (100% transmission), using the reagents and sodium chloride solution as a blank. The standard curve for proline is almost linear through the range given and is essentially linear at the lower concentration.

DETERMINATION OF BLOOD PROLINE

The proteins are precipitated by the rapid addition of 1 ml. of the plasma (or serum) to 2 ml. of 0.8% uranium acetate solution in a small (15 ml.) centrifuge tube. Mix thoroughly and centrifuge. Transfer 1.5 ml. of the clear supernatant to a colorimeter tube and add 0.25 ml. of nitroprusside-aldehyde reagent. Allow to stand two minutes and then add 0.25 ml. of 4% sodium carbonate solution. Read in the photocolorimeter after three minutes. The color has been developed on the equivalent of 0.5 ml. of the original sample; therefore the value read from the standard curve multiplied by two gives the "proline" level in micrograms per milliliter of fluid. Recoveries of proline added to blood have been carried out [4] with an error of less than ±5%. A comparison by eye of the color intensities of the fasting and postprandial samples is adequate if a simple semiquantitative determination of proteolysis and amino acid absorption is desired. The difference in color due to a threefold to fourfold increase in "proline" is appreciable. Even though the relationship of optical density to proline concentration is not exactly linear, a comparison of the optical densities of the two samples without conversion to the actual proline concentration is adequate for diagnostic purposes, especially since the postprandial sample when gelatin has been fed contains both proline and hydroxyproline, which are not quantitatively equivalent in the color reaction but are additive.

DETERMINATION OF GLYCINE

To compare the newly proposed method with the earlier method in which glycine was the index amino acid, parallel analyses were carried out for glycine and for proline. Glycine was determined as previously, by the method of Alexander, Landwehr, and Seligman.[3]

RESULTS AND COMMENT

The previous study [1] has shown that a relationship which may be used as a diagnostic procedure exists between the presence or absence of proteolytic activity in the duodenal fluid and ability or inability of the subject to digest a gelatin meal with a concomitant rise in the plasma glycine concentration. The data which have been accumulated in the present study have not been directed primarily toward the further substantiation of this observation but rather compiled to determine whether the determination of plasma proline by a simple colorimetric method can replace the more difficult glycine determination and also whether the plasma proline determination may be applied after casein test meals, where the glycine method is not applicable.

Several small groups of patients were studied, and in every case both plasma glycine and plasma proline were determined. There was no attempt to separate the groups on the clinical bases employed previously,

* "Apparent proline" refers to the fact that after a gelatin meal both proline and hydroxyproline are present in the blood. After a casein meal the increase is due only to proline. Normally the blood contains no detectable free hydroxyproline.

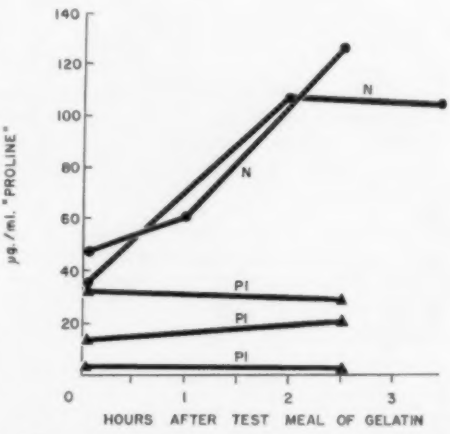
† Since sodium chloride intensifies color production, an amount of salt is added which will result in a final salt concentration corresponding to that anticipated in the estimation. In the present case the plasma NaCl has been assumed to be 0.6%.

Plasma Proline and Glycine Levels in Healthy Children and Children with Pancreatic Insufficiency Before and After Feeding of Gelatin or Casein

		Proline					Glycine				
		Mean Fasting Level			Post-prandial Level, Mean	Post-prandial-to-Fasting Ratios	Mean Fasting Level			Post-prandial Level	Post-prandial-to-Fasting Ratio
Subject	No. of Observations	γ/Ml.	S. D.*	Range			γ/Ml.	S. D.*	Range		
Healthy	14	24.8	±6.6	(13.8-32.5)	....	...	18.3	±2.95	(15.0-24.3)	....	...
P. I.†	14	14.1	±4.6	(8.0-23.0)	....	...	17.6	±5.1	(11.2-28.9)	....	...
Healthy after gelatin feeding	8	....	.....	.....	101.4	3.7	....	.....	.....	80.5	4.4
Healthy after casein feeding	4	....	.....	.....	76.7	3.2	....	.....	.....	19.4	1.2
P. I. after gelatin feeding	4	....	.....	.....	17.2	1.3	.. .	.....	.....	28.2	1.6
P. I. after casein feeding	4	..	.....	.....	21.0	1.5	.. .	.....	.....	19.0	1.1
P. I. after papain and gelatin feeding	8	....	.....	.....	52.8	4.0	.. .	.....	.....	54.9	3.0

* Standard deviation of the mean.
† P. I. refers to children with pancreatic insufficiency.

but they were separated instead into groups of (1) healthy children and (2) children with known cystic fibrosis of the pancreas having complete pancreatic enzyme deficiency. The proline and glycine fasting levels are shown in the Table. It is interesting that while there is no significant difference between the fasting glycine levels of healthy persons and of cystic fibrosis patients, the fasting plasma proline level of the latter is appreciably diminished. Some representative responses of the change in blood proline concentration after a gelatin meal are shown in the Figure.



Determination of plasma proline as a diagnostic procedure for pancreatic insufficiency. Typical responses in "plasma proline" following the administration of a gelatin test meal. *N* refers to response in healthy persons; *PI* refers to response in patients with pancreatic insufficiency.

A group of children with cystic fibrosis of the pancreas who showed no significant change in plasma proline after a test meal of either gelatin or casein were fed 250 mg. of papain ‡ with the meal. From the data shown in the Table it can be seen that the ratio of postprandial to fasting proline is restored to normal. In one case where the ratio without papain was 2.0 the administration of 200 mg. of the enzyme raised it to 3.85; administration of 400 mg., to 4.2, and of 800 mg., to 4.3. It is evident therefore that the administration of papain in adequate dosage restores normal intestinal degradation of gelatin as reflected in the proline and glycine plasma levels after feeding the combination of enzyme and protein. The rise in plasma proline and glycine in these patients indicates the ability of the patients with pancreatic insufficiency to absorb these amino acids. In a sense, this experiment serves as a control; it indicates the ability of patients with cystic fibrosis to absorb free amino acids unimpaired. In addition, the test suggests a clinical assay method for proteolytic enzyme preparations. Finally, the therapeutic effectiveness of pa-

‡ Supplied through courtesy of Dr. M. L. Tainter, of Sterling-Winthrop Research Institute, Rensselaer, N. Y.

pain in pancreatic insufficiency is suggested by the fact that the response observed in such patients when papain is fed along with protein is comparable to that normally encountered in healthy persons following a protein meal.

SUMMARY

A number of children with cystic fibrosis of the pancreas with complete pancreatic enzyme deficiency as well as a number of healthy children were studied to determine whether the response of their plasma proline levels to the feeding of either gelatin or casein could be used as a simpler and more generally useful diagnostic test.

A new simple method for the determination of plasma proline has been found suitable, and its application indicates that it can be used in conjunction with or that it may replace the glycine method.

The proline method has the advantage that it may be applied after casein or gelatin meals, whereas the glycine method is useful only after gelatin meals.

Children with cystic fibrosis of the pancreas with complete pancreatic insufficiency have a fasting proline plasma level much below that of healthy children, whereas the fasting aminoacetic acid levels are approximately the same.

The administration of a proteolytic enzyme preparation, papain, with the test meal of gelatin to patients with pancreatic insufficiency results in a significant improvement in protein digestion.

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Neuroblastomas in Infancy and Childhood

A Review of Ten Years' Experience

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Neuroblastomas in childhood are usually rapidly fatal. One of the highest survival rates has been reported recently, by Koop and co-workers,[2] as 31% for infants surviving 14 months or longer after diagnosis. The result of management of this disease has been so disheartening in spite of occasional reports of recovery that any improvement in survival rates deserves emphasis. The suggestion of Koop and co-workers that treatment consisting of surgical removal or maceration of the tumor results in better survival rates than surgical biopsy followed by x-ray radiation led us to reexamine our case material in the light of the surgical therapy suggested by these authors.

MATERIAL

A total of 25 cases of neuroblastoma, including 15 boys and 10 girls, were studied in Denver Children's Hospital during the past 10 years, 1945 through 1954. Of these cases, 20 (80%) were under 2 years of age, 5 (20%) between 2 and 7 years. Of our cases, 18 (72%) had primary retroperitoneal tumors; 6 (24%) were on the right side and 12 (48%) on the left. Six (24%) other children had primary retropleural tumors, and in one other case the primary site was not ascertained. Data on these cases pertinent to this paper are presented in Tables 1 and 2.

PATHOLOGY

The histological material of the primary tumor and the metastases from the 25 cases was studied. No new concepts were formed as a result of the review. Several points deserve reemphasis, however. It has long been recognized that a maturation progression is demonstrable in different tumors and also within a single neoplastic mass, as Wahl and Craig [5] and Blacklock [1] emphasize. What is more important, there is no evident clinical significance in this. The one associated tumor, the ganglioneuroma, is a fully differentiated neoplasm and is benign. So long as there is a malignant component present, the behavior of the particular neoplasm must be considered malignant. It can be hoped that an occasional case originally malignant may become completely differentiated, but this must be the exception rather than the rule. There was no apparent relationship of specific cell types with specific age ranges in our material, although Wilkins [6] states that the sympathogonioma (neurogonioma) arises in embryonic life or during the first year of infancy. We did not encounter this cellular type in our series.

COMMENT

From the study of our material it appears that if significant increases in the cure of this disease are to be realized, attention must be directed toward the discovery of this malignant tumor before there are signs or symptoms. It is significant that in six (24%) of our patients a tumor mass was palpated on routine physical examination before there were signs or symptoms referable to the neoplasm. Five of these patients are alive and are apparently well at least 14 months after diagnosis; the sixth patient (Table 1, Patient 7) died of radiation nephritis [8] 5 months after treatment, with no evidence of neuroblastoma at postmortem examination. Carefully done physical examinations may well call attention to the presence of the tumor

Submitted for publication Dec. 20, 1955.

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TABLE 1.—*Summary of Cases*

Patient	Age, 1st Admission	Sex	Presenting Complaints	Primary Tumor Location	Biopsy Site	Duration of Illness Before Diagnosis	X-Ray Evidence of Mass	X-Ray Evidence of Bone Lesions
1	23 mo.	M	Knee pain, masses on head; mass in neck	Left abdomen	Primary	4 wk.	Positive	Positive
2	7 yr.	F	Low-grade fever	Right chest	Primary	2 mo.	Positive	No bone survey
3	7 mo.	M	Abdominal distention	Right chest	Primary	3 mo.	Positive	Negative
4	2 yr.	F	Abdominal mass	Left abdomen	Primary	2 mo.	Positive	Negative
5	10 mo.	M	Listlessness, protruding eye	Right abdomen	Postmortem	1 mo.	Positive	Positive
6	6 yr.	M	Listlessness, weight loss	Right abdomen	Primary	6 mo.	Positive	Positive
7	18 mo.	M	Mass on routine examination	Left abdomen	Primary	Indefinite	Positive	Negative
8	5 wk.	M	Mass on routine examination	Left abdomen	Primary	6 wk.	Negative	Negative
9	18 mo.	M	Limp, then refusal to walk; pain, hip	Left abdomen	Primary	4 mo.	Positive	Negative
10	17 mo.	F	Mass on routine examination	Left abdomen	Primary	Indefinite	Positive	Negative
11	19 mo.	F	Refusal to walk	Left chest	Primary	8 mo.	Positive	Negative
12	7 wk.	M	Irritability, abdominal distention	Left chest and abdomen	Rib metastases	4 wk.	Positive	Positive
13	6 wk.	M	Vomiting	Left chest	Primary	5 wk.	Positive	Positive
14	1½ yr.	F	Unable to walk; difficult breathing	Right chest	Right parietal bone metastases	3 days	Positive	Negative
15	11½ mo.	M	Fever, refusal to walk	Right abdomen	Postmortem	6 mo.	Negative	No bone survey
16	2 yr.	M	Foot pain with limp	Not determined	Iliac crest metastases	2 mo.	Negative	Positive
17	4½ yr.	F	Back, knee, and shoulder pain	Left abdomen	Primary	3 mo.	Positive	Positive
18	22 mo.	F	Vomiting, abdominal distention	Left abdomen	Postmortem	3 wk.	Positive	Negative
19	16 mo.	F	Mass on routine examination	Left abdomen	Primary	Indefinite	Positive	No bone survey
20	14 mo.	F	Mass on routine examination	Right abdomen	Primary	Indefinite	Positive	No bone survey
21	5 yr.	F	Weight loss; listlessness	Left abdomen	Cervical lymph nodes	9 mo.	Positive	Positive
22	2 yr.	M	Fever, weight loss; drags leg	Left abdomen	Primary	3 wk.	Positive	Positive
23	5 yr.	M	Leg pain	Right abdomen	Primary	5 mo.	Positive	Positive
24	10 mo.	M	Weight loss; protruding eye	Left abdomen	Mass lateral to orbit	1 mo.	Positive	Negative
25	2 days	M	Mass on routine examination	Right abdomen	Liver metastases	Immediate postnatal	Positive	Negative

even before a mass can be visualized by x-ray examination. If a mass is discovered, its identification and proper treatment must not be delayed.

The discovery of an abdominal mass need not be the responsibility of the physician entirely. We are constantly reminded of the signs of early cancer in adults; in children early discovery is equally mandatory. Mothers should be tactfully instructed to examine their children's abdomens by light palpation at bathing or dressing times. The mother should not be alarmed into thinking the physician expects a mass to appear, but perhaps she could be told that the child's abdomen should be examined for masses as routinely as she may examine her breasts for masses.

A neuroblastoma often may be overlooked since its vague symptoms of low-grade fever, listlessness, leg aches, cough, and mild anemia occur in so many less serious pediatric diseases. Because of the insidious onset, the average interval between the time the child was first thought to be ill, presenting with one or more of the above signs or symptoms, and the time the diagnosis was made was

about three months. The greatest interval was nine months.

One sign which occurred often enough to be especially emphasized was the refusal of the child to use an extremity or the sudden appearance of a limp with or without the complaint of pain. This occurred in nine (36%) of our patients as one of the earliest indications of this disease, and is also recorded in the reports on neuroblastoma by Oberkircher and co-workers [3] and Uhlmann and von Essen.[4] Too often this complaint has been interpreted as indicating rheumatic fever in the older child or osteomyelitis in an infant. A thorough investigation should not be postponed when a small child with such findings is presented to the physician.

X-ray examination in all of our patients with chest lesions and in all but three of those with an abdominal mass was helpful in delineating the tumor mass.

Treatment of neuroblastomas at this hospital has consisted of surgery and radiation. These two forms of therapy have been applied individually or in combination either to the primary lesion or to metastatic sites, or to both. None of these forms of therapy has been uniformly effective. Details of the surgical technique and the attendant problems are beyond the scope of this paper, and the reader is referred to the report by Koop and co-workers [2] for this aspect of therapy.

In general, the technique of x-ray therapy now used at Children's Hospital in treating the primary lesion of neuroblastoma consists of giving 200 r (in air) per day, beginning the day following surgery and continuing until an estimated minimal tissue dosage of 1200 r has been given. The radiation is directed to alternate AP and PA ports, as small as possible consistent with the area of involvement. Large children with extensive abdominal involvement may require dividing the AP and PA fields into several ports. A similar course is repeated again in two months. Marrow depression is the limiting factor of the roentgen dosage and is probably responsible for the general debility which usually appears after about 1000 r have been given. Skin reaction and wound healing are not significant problems. Every effort is made to avoid irradiating more than one kidney. The use of a lateral port was discontinued after our one case of fatal radiation nephritis.[8] There has been no evidence of kidney injury in subsequent patients. Growth disturbance in the spine is visible, but minimal, in two of the surviving cases; this has not been serious enough to alter our concept of therapy. Liver metastases are treated if demonstrated; bone metastases are treated but usually are too extensive to be given adequate dosage and, therefore, respond poorly. Preoperative radiation is not favored, since the shrinking of the tumor mass has not facilitated surgical removal and proof of any other value of the radiation is lacking.

The variations in surgical and radiation therapy as used in our 25 cases are presented in Table 2. The most favorable results were obtained with the combination of excision of the primary tumor plus radiation to the primary site and metastasis. Only 1 of the group of 10 patients treated in this manner had obvious metastasis, and he died within six months after the diagnosis was made. Of the 10 patients so treated 3 are livng at least 18 months after the diagnosis was made. None of these had evidence of metastasis. Three other patients treated in like manner deserve mention. One (Table 1, Patient 2) of these died two years after the diagnosis with disseminated neuroblastoma. The second patient (Table 1, Patient 7) died of radiation nephritis five months after his course of treatment, and the third patient (Table 1, Patient 3) had the following course. A biopsy was done on a tumor of the chest wall, and the diagnosis of ganglioneuroblastoma made. Since further surgery was not considered feasible, radiation therapy was directed to the chest wall mass and to a mass in the right lower chest, posteriorly. The chest mass definitely had decreased in size when reexamined by x-ray two months after treatment was begun. Four months after the tumor was diagnosed a

radical dissection of the tumor and the chest wall was carried out. Four months later the patient returned to the hospital with generalized edema, ascites, and respiratory difficulty, and died within a few days, thus surviving eight months after the diagnosis was made. There was no evidence of any tumor tissue found at the postmorten examination; a mural thrombus of the right auricular appendage was found with multiple pulmonary emboli and infarctions. His signs, symptoms, and death are all attributable to right heart failure secondary to the pulmonary arterial occlusions. Radiation therapy was not incriminated in the death of this patient. The remaining three patients in this group died within six months of the time the diagnosis was made.

Seven of the remaining fifteen patients were not treated. All seven died. Of the eight patients who were treated other than by excision of the primary tumor plus radiation, only two have survived. The first (Table 1, Patient 19) of these two received a biopsy of the primary tumor followed by radiation to the primary site. Six months later a nodule appeared in the abdominal wall, and this was treated with radiation therapy. She has now survived two and one-fourth years since diagnosis and is without any evidence of neuroblastoma. The second patient (Table 1, Patient 25) was noted to have liver metastasis at laparotomy. Biopsy of the metastatic lesion was done followed by radiation therapy to the primary and metastatic site; he is symptomless now, 14 months after the diagnosis of neuroblastoma was made. This case is further evidence that liver metastases may not have so bad a prognostic import * as bone metastases.

X-ray examination of the long bones and the skull is of value in prognosticating the outcome of the disease. All of our patients with radiographic evidence of bone metastasis (52%) died. A skeletal survey is made as a part of the original diagnostic study for a neuroblastoma and serves as a base line for similar subsequent studies at six-month intervals. There is no correlation in our cases between the time of the initial onset of symptoms and the appearance of bone lesions.

It is of interest that in those children who appear to be cured of the disease, the ages at the time of discovery of the tumor ranged from 3 days to 18 months, with an average age of 9.8 months. In those patients who died, the ages at the time of discovery of the tumor ranged from 6 weeks to 7 years, with an average age of 28 months. These facts suggest that those children under 1 year of age who have this tumor have a better prognosis than those children 2 years of age or older.

TABLE 2.—*Therapy and Survival*

Management	Survival After Diagnosis: Death, 6 Mo. or Less	Death, 6 Mo. to 2 Yr.	Survivals*
Excision of primary tumor and radiation to the primary tumor and metastasis	5†	2‡	1 living 6 yr. 1 living 4⅓ yr. 1 living 1⅓ yr.
Biopsy of primary tumor and radiation to primary tumor	3	..	1 living 2¼ yr.
Biopsy of metastasis and radiation to primary tumor and metastasis	2	..	1 living 1⅓ yr.
Biopsy of metastasis only	3	..	.....
Biopsy of primary tumor only	2	..	.....
Radiation only to primary site and metastasis	1	..	.....
No radiation or surgery	2	..	.....

* All living patients have no evidence of neuroblastoma at this writing.
† One patient died of radiation nephritis.
‡ One died 8 months after the diagnosis with multiple pulmonary emboli; the other died 2 years after diagnosis with disseminated neuroblastomatosis.

* References 2, 4, and 7.

Eighty-nine per cent of the patients who died did so within the first six months after diagnosis of the tumor, and ninety-five per cent of those who died lived less than one year. This fact leads us to conclude that if the child survives 12 to 18 months after diagnosis and is still without evidence of the disease, he is most likely cured.

CONCLUSIONS

This study of neuroblastomas suggests that early diagnosis of these neoplasms is the most important factor in improving the survival rates of this malignant childhood tumor. Early diagnosis of the abdominal mass rests upon palpation of the mass before symptoms are present. It is in these cases only that treatment of any kind has been effective in our experience.

In addition to the three patients still living who were treated by excision plus radiation, three others appeared to have a response to this therapy, two dying less than a year after treatment without evidence of tumor on postmortem examination, and one dying two years after treatment with extensive metastatic lesions. This suggests that excision may have merit over biopsy, even though the small number of surviving cases in each group does not bear this out. Since each of our five living patients did receive radiation therapy, we cannot discount its role in the successful management of neuroblastoma.

SUMMARY

Twenty-five cases of neuroblastoma are presented.

Certain points in diagnosis and prognosis are discussed.

All our cures are in cases in which the abdominal tumor was palpated before symptoms were present.

No form of therapy has proved superior in our group of cases. Of 18 patients who were treated, 5 have survived at least 14 months. The survival rate is 28% in this group.

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Allergy in the Infant and Preschool Child

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A belief seems to have become entrenched in the professional mind that infants and young children are not suitable subjects for comprehensive allergy diagnostic procedures. This group has therefore been neglected, and we have little data with respect to their allergic status.

Buffum,* in his valuable studies on asthma in the first year of life, is one of the few investigators who showed that skin tests are valuable. Kaufmann [5] and Davis [6] also give evidence of the need for studying asthma in the infant. Glaser and Johnstone [7] actually project the idea that control of the allergic diseases should begin in the newborn period.

Infants and young children may outgrow their hypersensitivities spontaneously [8] or may develop an immunologic tolerance through continued natural contact. On the other hand, allergy that appears in the very young may persist into adult life.

A presentation of the findings in this age group, we believe, will encourage further intensive work and help to forestall or shorten the inroads of allergy in later years. To this end we should like to report on a comprehensive investigation of 64 infants and preschool children.† Twenty-seven were under 2 years of age, and the remainder ranged from 2 to 5 years. These children suffered from asthma, eczema, hay fever, or urticaria. Subjects with gastrointestinal symptoms were not included, because they require a somewhat different approach and do not ordinarily give positive skin reactions.

GENETIC INFLUENCE

Two of the children in this series were adopted. Of the remaining 62 families, 31 had positive family histories. This tallies favorably with the figures obtained by other investigators with adults suffering from allergy. Buffum ‡ found a somewhat higher incidence among asthmatic infants under one year, as did Clein [9] in his series of allergic infants. Fifty of our patients had their onset during the first year, ten during the second year, and four between two and five years. It has been postulated that the stronger the hereditary influence the earlier the age of onset. Since all the infants had so early an onset, we should have expected positive family histories more frequently than is found in allergics whose onset is later in life. Such, however, was not the case.

CONGENITAL ALLERGY

In the past we have demonstrated § that the human placenta is permeable to the passage of undigested food antigens. When pregnant women consume large amounts of

Submitted for publication Dec. 20, 1955.

Presented at the Scientific Session of the Section on Allergy at the 24th Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 3, 1955.

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* References 1-4.

† Ten of these patients, for one reason or another, dropped out before the studies were completed. However, we retained their records for information relative to many facets of the problem. So far as the skin tests were concerned, 54 infants were studied comprehensively.

‡ References 1-4.

§ References 10-12.

highly antigenic foods, particularly during the third trimester, undigested antigens may be transferred to the fetal circulation and may give rise to active sensitization of the fetus. The fetus may also be sensitized passively by the passage of antibodies from the circulation of an allergic mother to the fetal circulation via the placenta.

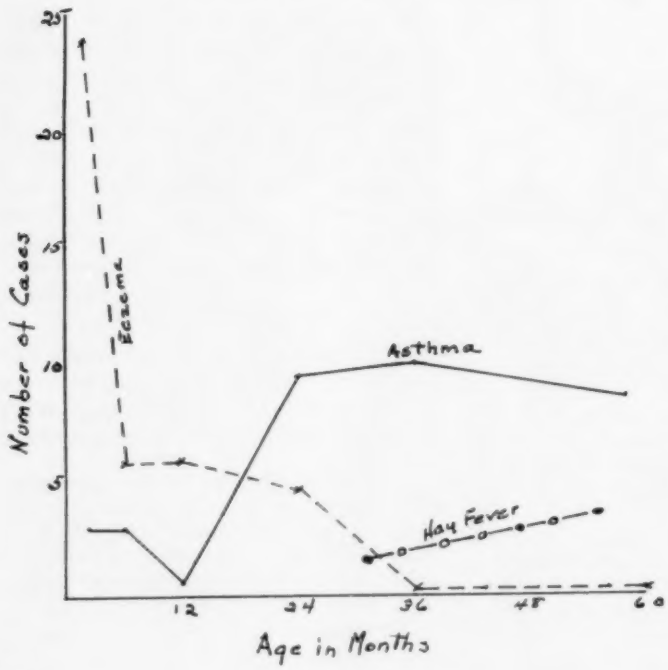
Clinical manifestations of congenitally acquired allergy are first exhibited either (1) when the infant ingests the food for the first time either as a regular feeding or accidentally from utensils or dishes used in preparing such foods or (2) through contact with persons who have handled or eaten the offending food. Here a dermal reaction might ensue when the hypersensitive infant is kissed or handled by a person who has just eaten or handled the food to which the infant is sensitive. Thus the reaction essentially would be a contact dermatitis to foods through contaminated lips or hands.

A positive history of excessive indulgence in specific foods cannot always be obtained from the mother. In our present series 17 (27%) of the 64 patients gave evidence by skin test of sensitivities to foods which they had not previously ingested. In certain instances clinical manifestations such as vomiting and diarrhea were observed. It is interesting to note that all of the infants manifested eczema.

INCIDENCE OF ALLERGIC DISEASE

It will be noted in the Figure that there was a high incidence of eczema and a lower incidence of asthma in the first year. Few cases of eczema started after the third year.

Many of the so-called asthma cases in the first year were diagnosed as asthma elsewhere and were subsequently found to be not true asthma. These pseudoasthmatic cases were included because statistically they are still on the clinical record as asthma. The dip in the incidence of asthma in the second year, therefore, may be attributed to errors in diagnosis in the first year. Congenital cardiorespiratory anomalies and



Incidence of allergic disease in the young age group.

bronchial obstructive syndromes, producing wheezing, account for these errors in diagnosis.

The incidence of the allergic dermal-respiratory syndrome, i. e., the development of respiratory allergy subsequent to the dermal allergy, in this young age group was 25%, as compared with 33% in children of all ages previously reported.[13]

In the Northeastern section of the country, from which most of our cases stem, there is practically no hay fever in the first two years. Only in the third year do we begin to note the appearance of hay-fever symptoms. This is logical if one reasons that about two seasons of exposure to pollen are necessary for establishment of hay fever. However, young infants may suffer from pollen asthma without any signs of true hay fever.

Of the 64 patients studied, 30 (47%) gave a history of episodes of urticaria at one time or another. There was no instance of chronic urticaria in this group. Urticaria is a commonly recurring syndrome in early infancy and is not a fixed entity, as is eczema or asthma. It is usually of mild order, unless it occurs as a serum sickness or serum-sickness-like episode.

It would appear that allergic diseases in the young show a predominance of eczema in the first year, followed by a fall in eczema and a rising incidence or asthma and hay fever as age progresses.

INCIDENCE OF ALLERGENIC FACTORS

To determine the offending factors causing the allergic syndrome, these patients were subjected to elaborate test procedures. The subjects were tested with 236 foods by the scratch method and with 128 inhalant substances by the intradermal method. The intradermal test materials included a rather large variety of seasonal pollens, most of the common inhalant substances, and a goodly number of molds and bacteria.

Fifty-four infants who remained with us for longer than one year were retested after the first year and two years later to determine whether new sensitivities had developed or old ones had disappeared. Retests after this period were done wherever the conditions warranted it.

An analysis of the distribution of sensitivities among 49 children with eczema and asthma presented in Table 1 discloses that 12.2% reacted to foods alone, 4.1% reacted to pollens alone, and 28.5% reacted to miscellaneous inhalants alone. The majority, 55.2%, reacted to combinations of foods, inhalants, molds, and pollens.

It is difficult to assign a specific allergen to the appearance of urticaria.

TABLE 1.—*Distribution of Sensitivities in Eczema and Asthma* *

	Eczema	Asthma	Eczema and Asthma, %
Foods alone	4	2	12.2
Pollens alone	0	2	4.1
Inhalants alone †	6	8	28.5
Foods, inhalants, molds, and pollens	17	10	55.2

* In this group 4 eczema and 12 asthma cases also reacted to bacterial antigens.
† Other than pollens and molds.

TABLE 2.—*Incidence of Skin Reactivity*

Age, Yr.	Cases, No.	Food, %	Pollens, %	Inhalants, %	Molds, %
0-1	10	100	20	70	10
1-2	17	76	59	82	30
2-3	17	70	85	90	47
3-5	20	60	88	90	50

The incidence of etiologic factors in the young age group is characterized by a decreasing sensitivity to foods and increasing sensitivity to pollens with age progress. The miscellaneous inhalants rate relatively high throughout, whereas the incidence of mold sensitivity is moderate. These findings are presented in Table 2.

FOOD SENSITIVITIES

An analysis of food allergens is made here to show the complexity of the problem and to emphasize the need for complete testing in this young age group.

The majority of allergic children react to multiple foods. Only 12.2% of the eczema

and asthma group (Table 1) reacted to foods alone, and no child reacted to a single food.

In Table 3 is listed the number of reactions that were obtained to the various food substances.‖ Some broad generalizations may be of interest. Certain groups, such as fish, eggs, and cereal grains, produced reactions very frequently. The mustard, rose, nightshade, walnut, and pea families, which include a multiplicity of allergens, were next in order. They were followed by milk and the citrus family. Chocolate, which has always been regarded as a frequent offender, produced reactions in only 11% of cases.

In relation to a few of the more frequently employed foods, certain factors may be garnered that will influence diagnosis and treatment.

Milk.—Eighteen (28%) reacted to milk or one of its constituents. Four of these reacted to casein both clinically and by skin test; the remaining fourteen reacted to the whey constituents alone.

TABLE 3.—*Reactions to Various Foods*

Food	Cases, No.
Fish	37
Egg	31
Cereal grains *	30
Mustard family †	30
Rose family ‡	27
Nightshade family §	25
Walnut family ‖	23
Pea family ¶	22
Milk	18
Citrus family ‡	18
Parsley family **	18
Gourd family ††	17
Lily family ‡‡	15
Fowl	12
Cashew family §§	11
Hazelnut	9
Pineapple	8
Mint	7
Sweet potato	7
Chocolate	7
Olive	6
Mushroom and yeast	6
Fig	6
Cinnamon	6
Brazil nut	6
Banana	5
Spinach and beet	5
Paprika	5
Ginger	3
Date and coconut	3
Tea	3
Okra	2
Nutmeg	1

* Barley, corn, oats, rice, rye, wheat, malt.
† Broccoli, Brussels sprouts, cabbage, cauliflower, kale, horse radish, kohlrabi, mustard, radish, rutabaga, turnip, water-cress.
‡ Almond, apple, apricot, blackberry, cherry, peach, pear, plum, prune, quince, raspberry, strawberry.
§ Cayenne, green, and red pepper; eggplant; tomato, white potato.
‖ Butternut, hickory, pecan, black walnut, and English walnut.
¶ Black-eyed pea, Jack bean, kidney bean, licorice, lima, lentil, locust bean, navy bean, pea, peanut, soybean, string bean.
‡ Grapefruit, lemon, lime, orange, tangerine.
** Aniseed, caraway, carrot, dill, celery, celeriac, parsley, parsnip.
†† Cantaloupe, casaba, cucumber, honeydew, pumpkin, squash, watermelon.
‡‡ Asparagus, chive, garlic, leek, onion.
§§ Cashew nut, mango, pistachio.

TABLE 4.—*Relation of Milk to Other Allergens*

Allergens	Cases
Milk alone	0
Milk and other foods	1
Milk and inhalants *	1
Milk, other foods, and inhalants	16

* Inhalants here include pollens, molds, miscellaneous inhalants.

It has been our experience that only casein-sensitive persons cannot tolerate cow's milk in heat-denatured form. Therefore the majority of these patients safely consumed heat-treated milk, such as Similac or other forms of evaporated milk. Less than one-quarter of the milk-reactors required a milk substitute such as Mull-Soy or other forms of soybean preparations.

It is of interest to note (Table 4) that in no case was there a reaction to milk alone. From this observation we conclude that no milk case can be treated comprehensively by merely correcting the milk situation.

Egg.—In 31 of the cases (48%) positive reactions were obtained to whole egg or some fraction. This finding compares favorably with Hill's [14] series, for in a study of 300 children he found a positive reaction to egg in 131 subjects (43%). In 11 of our patients there was a positive reaction to egg white albumen, egg yolk, or both, and ovo-

‖ The tests were carried out with individual allergens. However, frequently positive reactions occurred with several allergens within a botanical or biological family. For clarity, in our Table we have combined these individual allergens within the family group.

mucoid. Those who reacted to ovomucoid could not tolerate hard-boiled eggs, whereas those who reacted only to the albumen fraction did tolerate this form of heated egg. The three major protein fractions of egg should be used for testing purposes.

Cereal Grains.—Thirty (46%) showed positive reactions to one or more cereal grains. Wheat or one of its fractions elicited reactions in 18 subjects. In seven instances there were reactions to two or more of the wheat proteins. In three patients positive reactions were elicited to three or more cereals. No reactions were obtained to rice.[15]

TABLE 5.—*Reactions to Various Pollens, Inhalants, and Molds*

Sensitivity	Cases
Weeds:	
Ragweed alone	0
Ragweed with other unrelated allergens	39
Ragweed as the only weed	13
Ragweed with other weeds	28
Weeds without ragweed	5
Ragweed with Pyrethrum	11
Pyrethrum without ragweed	2
Ragweed with tobacco	12
Tobacco without ragweed	1
Grasses:	
Grass alone	0
Grass with other allergens	34
Timothy as the only grass	0
Timothy with other grasses	22
Grasses without timothy	14
Trees:	
Trees alone	1
Reaction to a single tree	9
Trees with other allergens	33
Inhalants:	
Inhalants alone	12
Inhalants with other allergens	40
Molds:	
Molds alone	0
Molds with other allergens	36
Inhalants and molds	2
Trees, grasses, weeds, molds, and inhalants	24

Fish.—Reactions to fish were obtained in 37 (58%) patients. The majority of these, 33, showed positive reactions to salt-water fish, 20 reacted to fresh-water fish, and 14 to shellfish. Nine showed positive reactions to all three groups. Six patients reacted to 11 or more fish, one reacting to as many as 26.

Citrus Family.—The citrus fruits provoked positive reactions in 18 patients (28%). Of the 18 patients, 11 reacted to orange, 8 to lemon, 5 to grapefruit, 4 to lime, and 1 to tangerine. Seven patients gave positive skin reactions to two or more members of this family and three patients to three members.

RELATIONSHIPS OF SENSITIVITIES TO VARIOUS POLLENS, INHALANTS, AND MOLDS

In Table 5 it is noted that all of the children reacting to ragweed also responded to other allergens. Ragweed occurred as the sole weed offender in only 13 cases. It appeared in conjunction with other weeds in 28 cases. A number of subjects gave skin reactions to other weeds without reacting to ragweed.

Practically all of the patients who were sensitive to ragweed also reacted to botanically related Pyrethrum and tobacco.

There were no instances of sensitivity to grass alone. The oft-repeated statement that timothy is the dominant representative of grass sensitizers has led to the conclusion that it is sufficient to treat only with timothy. In no instance did we find timothy as the sole offender; the majority of patients reacted to other grasses as well. A number of patients reacting to grass pollens did not give dermal reactions to timothy.

Tree-pollen sensitivity, however, does at times stand alone. In a number of instances there was sensitivity to a single tree pollen.

A fair number of patients reacted to inhalants alone. This can be assumed to be due to concentrated and close contacts with feathers, cotton linters, animals, pets, etc. However, the majority (Table 6) reacted also to other allergens.

There were no instances of sensitivity to molds alone.

Twenty-four of the children reacted to one or more allergens in each group, i. e., trees, grasses, weeds, molds, and inhalants. This again emphasizes the preponderance of multiple sensitivities.

EOSINOPHILIA

Thirty-three patients (52%) showed an elevation of eosinophiles in the blood at one time or another. The range varied from 5% to 33%. We observed that the count might be normal at one time and show a rise at another. In all of the cases in which eosinophilia was not present at a single examination, at least four samples of blood had been examined.

Thirty-seven children presented adequate smears for the study of nasal eosinophilia (Hansel method). Thirty-three (89%) of these thirty-seven showed the presence of nasal eosinophilia at one or another time.

TABLE 6.—*Reactions to Various Inhalants*

Inhalant	Cases
Feathers	37
Cottonseed	33
Cat hair	27
Dust	24
Wool	21
Hog hair	20
Dog hair	20
Silk	19
Kapok	17
Rabbit hair	16
Cattle hair	15
Orris root	14
Pyrethrum	13
Tobacco	13
Goat hair	9
Flaxseed	8
Castor bean	5

With superimposed infections, the nasal cytology changed to a preponderance of neutrophiles. Thus we are enabled to differentiate between allergic and infectious episodes.

The repeated finding of nasal eosinophilia should suggest potential allergy.

BONE MATURATION

Studies on bone maturation showed 20 (31%) had a definite retardation as determined by fluoroscopy and/or x-ray.

RESULTS OF COMPREHENSIVE TREATMENT IN THE 64 INFANTS AND YOUNG CHILDREN

Fifty-one children responded to treatment. Six of these had eczema that we considered cured, for in this syndrome we have objective evidence of a complete remission of the condition. Three patients developed hay fever in the course of our studies and responded to therapy.

The duration of treatment varied. The majority of patients (41) were treated for more than four years. Ten responded to treatment in a shorter period. Thirteen did poorly, but of these ten dropped out before studies were completed. However, three did poorly despite all our efforts and also dropped out.

COMMENT

Our observations of these infants and young children corroborate certain trends and facts which have been established for allergic children of all ages. On the other hand, certain findings have been revealed that have an aspect of novelty.

The early age of onset of allergy in these cases was not influenced by a particularly strong positive family incidence.

Congenital transmission of sensitization in utero may explain the explosive allergic response that occurs in certain infants partaking of a food for the first time. When positive skin reactions are obtained to foods prior to actual ingestion by the infant, the assumption is that the allergic status is due to either active or passive sensitization in utero. We cannot postulate that specific food sensitivities have been inherited germinally, because no proof has been presented to support such a theory. Nor has the theory been proved that such sensitivities may result from passage of antigens through the breast milk.

For the present, skin testing offers the best means to determine the offending allergens in the individual case. This holds true for the child under 5 years as well as those who are older. A positive dermal reaction does not in every instance indicate that the patient will present some form of clinical manifestation upon each contact with the specific offending substance. We believe, however, that all positive skin reactions, especially in the young, should be considered as evidence of potential clinical reactivity.

The great number of skin reactions elicited in this group of young children may at first appear astonishing, but when we realize that the young infant is exposed to more experiences with new antigens than the adult, for during infancy he is more susceptible to the passage of native antigens into the blood stream, it does not seem so surprising.

Although all of the infants under one year of age did react to foods, many also reacted to inhalants, pollens, and molds as well. During the first five years we noted a gradual diminution in food sensitivity, a marked rise in pollen sensitivity, a consistently high incidence of sensitivity to inhalants, and a moderate incidence of mold sensitivity.

Our survey indicates that multiple sensitivities are the rule. Seldom does one encounter a patient who is sensitive to milk or some other food, for example, who does not have concurrent sensitivity to one or more of the inhalant allergens. In view of this significant finding, it is foolhardy to treat a young infant for only one or another obvious factor. To achieve effective results, all of the child's sensitivities must be taken into consideration in planning therapy.

Milk, which in the past was considered one of the prominent sensitizers, appears of less importance in our series. This we attribute, and we believe justifiably, to the fact that the preponderant number of infants today are fed heat-denatured milks, such as Similac or other evaporated milks. If we had included gastrointestinal symptoms as allergic manifestations in this study, the incidence of milk allergy would undoubtedly have been greater.

Of importance in the diagnosis of early and doubtful cases of respiratory allergy is the nasal cytology. Since this evidence aids us in differential diagnosis, we can pinpoint those persons who are truly allergic and thus have the opportunity to study them at the initiation of their difficulties rather than waiting until they develop a full-blown and intractable allergic state.

An increased number of eosinophiles in the blood is not as reliable an indication of allergy.

In our series at least every third infant showed evidence of bone retardation. We believe that retardation of bone maturation suggests hypometabolism. In the majority of such cases, we have found clinically that the judicious use of desicated thyroid helped in raising resistance to infection, overcoming fatigue, and correcting a dry, irritated, and infection-prone skin.

The study of allergy in this comprehensive manner in the infant and young child is rewarding. There are few chronic diseases in which a reversal from pathologic to normal physiology can be consummated, as can be achieved in allergy. The rehabilitation of a young allergic cripple is a truly gratifying experience and should forestall or shorten the inroads of allergy in later years.

SUMMARY

The age of onset of allergy does not appear to be controlled by hereditary factors, for the incidence of inhertance in this young age group was no greater than is found in older allergic persons.

Evidence for congenital allergy (sensitization in utero) was found in 27% of the cases.

It would appear that allergic diseases in the young show a predominance of eczema in the first year, followed by a fall in eczema and a rising incidence of asthma and hay fever as age progresses. No cases of true hay fever occurred prior to the third year (in the Northeastern section of the country). Pollen asthma, however, did appear before the third year.

The incidence of etiologic factors in this group is characterized as age progresses by a decreasing sensitivity to foods and an increasing sensitivity to pollens. The incidence of sensitivity to miscellaneous inhalants is relatively high, whereas that of mold sensitivity is moderate.

In the first year, 100% of the patients reacted to foods alone or in combination with other allergens. By the fifth year this was reduced to 60%.

Chocolate was shown to be an infrequent offender.

Milk sensitivities occurred in 28% of the cases. None of these patients reacted to milk alone. The majority reacted to the whey proteins. Less than one-quarter reacted to the casein fraction. Only this latter group required milk substitutes. The majority of milk reactors tolerated heat-treated milks.

Forty-eight per cent reacted to egg proteins.

Forty-six per cent reacted to one or more cereal grains. None reacted to rice.

Fifty-eight per cent reacted to seafoods, all reacting to more than one.

Twenty-eight per cent reacted to citrus fruits.

No patient reacted to ragweed alone. Practically all reacting to ragweed also reacted to Pyrethrum and tobacco.

No patient reacted to grass pollen alone. In no instance was timothy the sole offending grass.

Tree pollen sensitivity at times occurred as the only pollen sensitivity.

The majority of miscellaneous inhalant sensitivities occurred with other sensitivities but occasionally these inhalants were the sole offenders.

Mold sensitivity occurred always in conjunction with other sensitivities.

Nasal eosinophlia was found to be an important aid in the early diagnosis of allergy and occurred in 89% of the patients.

Thirty-one per cent of the children showed evidence of retardation of bone maturation.

The majority of the cases responded well to a multifaceted therapy.

The rehabilitation of the young allergic cripple should aid in the prevention and reduction of allergy in later years.

CONCLUSIONS

Because of the large amount of specific data that can be obtained in this early age group we believe that infants suffering from allergy should be skin-tested early and studied comprehensively.

There are few chronic diseases in which a reversal from pathologic to normal physiology can be consummated, as can be achieved in allergy. The rehabilitation of a young allergic cripple is a truly gratifying experience and should forestall or shorten the inroads of allergy in later years.

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Renal Tubular Disease with Nephrocalcinosis

Report of Two Unusual Cases

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Disorders of renal tubular function have received increasing attention in recent years, both from the clinical standpoint and because of their importance in clarifying renal tubular physiology. The present report concerns two patients, both of whom showed evidence of renal tubular disease together with renal medullary calcification (nephrocalcinosis). The clinical manifestations, however, were strikingly different and included certain unusual and confusing features which may be of interest.

REPORT OF CASES

CASE 1.—A boy aged 8 weeks was admitted to the hospital because of vomiting and failure to thrive, with hematemesis on the day of admission.

The patient was the product of the mother's fourth pregnancy, which was complicated by mild toxemia. There was no relevant family history. Delivery, at another hospital, was spontaneous. The birth weight was 2880 gm. The baby was discharged on the seventh hospital day, apparently in good condition.

Progress after discharge, however, was consistently unsatisfactory. Frequent vomiting occurred, which was not projectile and was unrelieved by formula changes. The vomitus was noted to be brown in color on one occasion. Marked constipation, but no melena, occurred. At one month of age the baby weighed 2840 gm. During the following month vomiting continued with increasing severity, and on the day of admission profuse vomiting of altered blood occurred.

Physical examination revealed an acutely ill, shocked infant, showing marked wasting and dehydration. Weight 2610 gm. Temperature 96 F, pulse 140. Examination otherwise was negative, and no pyloric tumor was felt. During examination the baby vomited a further large amount of altered blood.

Submitted for publication Dec. 27, 1955.

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Investigations.—Hemoglobin 9.8 gm. per 100 cc.; WBC 27,000, with 15,900 neutrophiles. Urinalysis showed a trace of albumin, with 1-2 red and 1-2 white blood cells per high-power field. Plain x-ray films of the chest and abdomen showed no abnormality. Further investigation was postponed owing to the infant's poor general condition.

A provisional diagnosis of gastrointestinal bleeding due to hiatus hernia or pyloric stenosis was made, and symptomatic treatment was started with blood transfusion and intravenous fluids. The baby continued to vomit small amounts of altered blood for a few days, but his general condition improved considerably. On the third hospital day x-ray examination showed free regurgitation of opaque medium up the esophagus in all positions (Fig. 1), apparently supporting the admission diagnosis of gastroesophageal incompetence due to hiatus hernia or chalasia of the esophagus.[1] There was no evidence of pyloric obstruction. Accordingly, antacids and thickened feedings were prescribed, and the baby was nursed in the upright position.

In spite of these measures, vomiting and dehydration recurred. Dyspnea was present, and it was noted that the baby voided frequently in spite of marked dehydration. Serum chemistry values showed CO_2 content 5.7 mM/liter, Cl 120 mEq/liter, NPN 31 mg/100 cc. The urine pH, measured simultaneously, was 7.0.

Fig. 1 (Case 1).—Barium swallow demonstrating free reflux of opaque medium from the stomach into the esophagus.

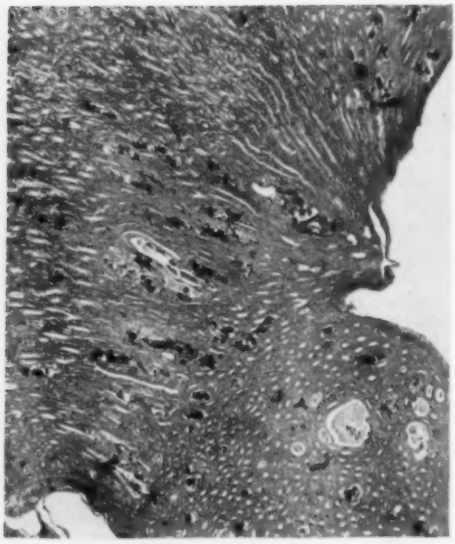

Fig. 2 (Case 1).—Medulla of kidney including portion of pelvis showing peritubular deposits of calcification (black). Hemalum, phloxine, saffron; reduced approximately ⅓ from mag. × 22.

A second diagnosis of infantile renal acidosis was made, and treatment was started with the sodium citrate-citric acid mixture recommended by Lightwood and co-workers,[2] containing 6 gm. of sodium citrate per day. Four days later the baby was again clinically improved: Serum CO_2 was 16.3 mM/liter, Na 141 mEq/liter, K 5.8 mEq/liter, Cl 110 mEq/liter, NPN 27 mg/100 cc., Ca 8.8 mg/100 cc., P 4.5 mg/100 cc. Intravenous pyelography revealed normal excretion of dye, and no renal calcification was observed. The urine showed a trace of albumin, with 2-4 white blood cells per high-power field. Escherichia coli was cultured from a voided specimen on one occasion.

In spite of the initially encouraging response, including an increase in weight to 4500 gm., improvement was not maintained. Acidosis was never wholly controlled, and increasing the dose of citrate to 8 and then 12 gm. per day caused edema and diarrhea. A persistent unexplained fever occurred which did not respond to antibiotics. Anemia recurred and was treated with blood transfusions. A second x-ray examination of the esophagus failed to demonstrate the reflux noted in previous films. On the 86th hospital day the baby suddenly developed severe diarrhea and vomiting with high fever, and he died on the 88th hospital day.

Autopsy revealed an emaciated and dehydrated infant weighing 4300 gm. The entire colon showed an edematous and hemorrhagic mucosa, and the lumen contained feces and blood. There was no evidence of gastric ulceration, pyloric stenosis, or hiatus hernia. The kidneys were of normal appearance and had a normal combined weight of 50 gm. The capsule was glistening and stripped readily. The cut surface of both kidneys revealed linear deposits of yellowish-gray material in the medulla, measuring about 0.3 cm. in length. The mucosal surface of both pelves was smooth and glistening. The remaining organs, including the brain, showed little of note on gross examination. E. coli, Serotype 0111, was cultured from the spleen, heart, lungs, and trachea.

Microscopic Findings (Figs. 2 and 3).—The lungs showed fairly widespread multifocal alveolar pneumonia as well as a moderate number of platelet

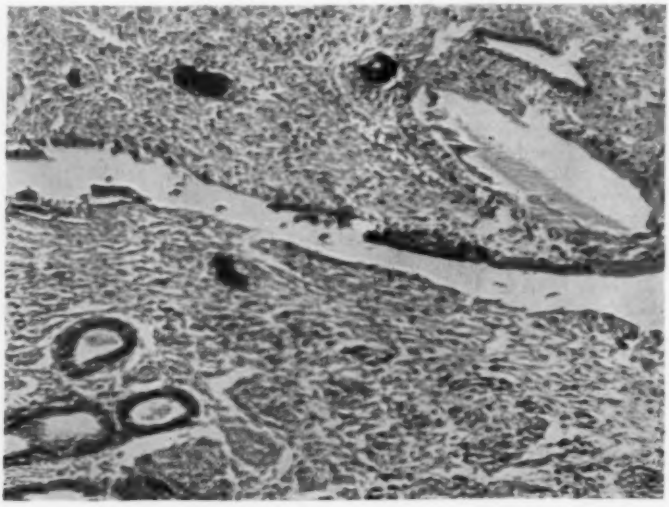

Fig. 3 (Case 1).—Prostatic duct showing deposits of iron-calcium complexes (black). Pressian blue method for iron; reduced approximately 1/5 from mag. × 100.

thrombi scattered throughout the lung veins. The bone marrow and costochondral junction showed no abnormality. There was a moderate right otitis media and a minimal exudate in the left middle ear. The parathyroids were microscopically normal. The liver showed minimal periportal fatty metamorphosis associated with minimal hemosiderosis. The spleen showed no definite evidence of sepsis, and there was no evidence of iron pigment present.

Sections of the large bowel from the cecum to the rectum showed an extremely hemorrhagic and edematous mucosa and submucosa. Numerous markedly dilated veins stuffed with red blood cells were present in these areas. No inflammation or ulceration was present. The lower ileum showed similar but less marked changes, while the jejunum was normal. Sections of the mesentery demonstrated that the large-bowel lesion was the result of recent noninflammatory thrombosis of the veins supplying the involved bowel. This was probably secondary to dehydration and infection. The mesenteric lymph nodes were atrophic, and a number of them were stuffed with red blood cells and showed a minimal acute lymphadenitis.

The kidneys showed moderately extensive calcification in the medulla (Fig. 2). This calcification was extratubular, being situated in the interstitial tissues and/or within the basement membrane of the collecting tubules. Many of the masses bulged into, distended, and obstructed the lumens of the tubules. The tubules of the papillae were frequently markedly distended and also contained protein casts in their lumens. Small papillary masses of calcified material projected from the surface of the papillae into the lumen of the pelvis.

Many of the calcified masses were surrounded by proliferating fibroblastic tissue, but there was no real inflammatory reaction, as only an occasional histiocyte was seen. No giant cells were seen. The lesion was associated entirely with the collecting tubules.

The cortical portion of the kidney showed no glomerular lesion. Occasional intratubular (epithelial) calcification was seen which was associated with minimal tubular necrosis. This minimal lesion was probably associated with the terminal diarrhea and vomiting and was quite different histologically from the principal lesion present in the medulla.

In summary, the findings in the medullary portion of these kidneys are similar to those previously described in this condition, particularly by Butler, Wilson, and Farber [3].

An accidental histological finding of interest was the presence of minimal focal calcification of the ejaculatory ducts of the prostate (Fig. 3). This calcification was identical to that present in the medulla of the kidneys, occurring just outside the epithelial layer. This was the only extrarenal calcification found at autopsy.

CASE 2.—A boy aged 4 years was admitted to the hospital because of tetany of 24 hours' duration and a recent generalized convulsion.

The patient was the first child of healthy parents. There was no relevant family history. Pregnancy and delivery were normal. The birth weight was 3470 gm. The child was breast-fed for two months, then was placed on an evaporated milk formula. Until 13 months of age he refused solid foods, and his diet consisted wholly of milk. Vitamin supplements were given irregularly. At 6 months he weighed 6150 gm. At about 9 months, growth appeared to slow down, and since then he had always been small for his age. He sat up at 4 months, walked and talked at 13 months, and was toilet-trained by 2 years. Infantile eczema started at the age of 3 months. His parents stated that he was "allergic" to eggs, cats, and dogs. He was noted to be always thirsty, and drank a quart of milk a day, in addition to quantities of water. No polyuria or nocturia had been noted.

Between the ages of 6 and 18 months, he attended the hospital outpatient department on five separate occasions, with attacks of vomiting, diarrhea, and fever. On each occasion an upper respiratory infection was found, and the symptoms subsided promptly with antibiotic therapy.

At the age of 3 years he developed a further attack of fever and vomiting and the parents noted that his hands and feet were stiff and painful. However, the significance of this complaint was not appreciated, and antibiotic therapy was prescribed, with prompt relief of symptoms. Two days before admission he developed fever, with cough, vomiting, and diarrhea. Stiffness of the hands and feet recurred, and he had a generalized convulsion three hours before admission.

Physical examination revealed a small, fairly well-nourished child. Height, 90 cm.; weight, 12.0 kg.; temperature, 100 F. There was a dry eczema in the flexures. Carpopedal spasm and Chvostek's sign were present. There was a right catarrhal otitis media. The chest was clear, and the kidneys were not palpable. The fingernails were normal. No other abnormality was noted on physical examination.

Investigations.—Hemoglobin 11.0 gm. per 100 cc. White blood cell count 13,700, with marked polymorphonuclear leucocytosis. Serum chemistry: CO_2 content 16.3 mM/liter, K 4.3 mEq/liter, NPN 21 mg/100 cc., Ca 5.8 mg/100 cc., P 4.5 mg/100 cc. Alkaline phosphatase 1.39 mM. units/liter (normal 1.0-5.5). Chest x-ray showed partial consolidation of the left lower lobe. Urine: albumin, nil; rare RBC and WBC; no casts seen.

Treatment consisted of penicillin and an intravenous infusion of 5% dextrose containing 2 gm. of calcium gluconate. Five hours later all tetanic manifestations were relieved. The patient had no further vomiting or fever.

Subsequent Investigations.—Blood chemistry: Repeated determinations of K, Cl, NPN, and phosphatase gave normal results. Values for total CO_2 (mean 21; range 18-25 mM/liter) and Na (mean 137; range 128-146 mEq/liter) were slightly low. After the initial normal value, serum P tended to be high (mean 6.2; range 5.0-7.2) and serum Ca low (mean 9.1; range 8.2-10.0). None of these values however, was consistently abnormal. Urine: pH 6.5-7.5, specific gravity 1.004-1.006, albumin nil, sugar nil, few RBC, 2-4 WBC per high-power field, occasional granular casts. Sulkowitch 1+, 24-hour excretion of amino acids normal. Mosenthal concentration-dilution test: specific gravity 1.004-1.007. Urea clearance 24 cc/minute/1.73 sq. m. Renal phosphorus "clearance" increased 100% following injection of parathyroid hormone, 50 units/square meter, indicating a normal tubular response.[4] Administration of ammonium chloride, 12 gm/square meter/day for six days caused a fall in urine pH from 6.2 to 5.5 and increase of ammonium excretion from 3 to 27 mEq/24 hours. The child showed a normal response to acetazoleamide (Diamox), suggesting that renal carbonic anhydrase activity was normal.*

X-Ray Examination.—Intravenous pyelogram. The kidneys appeared smaller than average. On both sides there were irregular scattered fine points of calcification throughout the medulla, and also in the cortex to a smaller degree. Dye appeared in good concentration at three minutes and was completely removed in two hours. There was slight dilatation of the calyces on both sides. Retrograde pyelography revealed mild hydronephrosis on the right side without evidence of obstruction. Films of the bones, including arms, legs, and skull, showed no evidence of metabolic bone disease.

Progress.—Subsequent hospital course was uneventful, and the patient was discharged on the 24th hospital day. At follow-up three months later, he was symptom-free. Height, 92 cm. Weight, 13.6 kg. Chemistry values: Na 140 mEq/liter, K 4.6 mEq/liter, Ca 9.3 mg/100 cc., P 4.9 mg/100 cc., phosphatase 4.1 mM. units/liter.

COMMENT

In 1935, Lightwood [6] described renal medullary calcification in a series of infant autopsies and correlated this finding with a clinical syndrome including failure to thrive, constipation, and anorexia. In 1936, Lightwood and co-workers [7] and Butler and co-workers [8] independently described cases showing dehydration and acidosis with nephrocalcinosis at autopsy. Several reports of infantile idiopathic renal acidosis have since appeared.† Symptoms commonly start during the second half of the first year and include anorexia, vomiting, constipation, and failure to gain weight. The urine commonly contains a trace of albumin and an increased number of white blood cells, and the pH is alkaline or weakly acid in spite of systemic hyperchloremic acidosis, this constituting an important diagnostic feature. Renal medullary calcification is demonstrable radiologically in some cases.

Case 1 provides an example of this group. The early onset of vomiting in the second week of life and hematemesis were unusual features and may have been due to the associated gastroesophageal incompetence, which may have represented either an independent primary lesion or a complication of prolonged vomiting and dehydration, as has been recently suggested.[13] The association of hematemesis with renal acidosis has not been previously described. In view of the widely held belief that most examples of this esophageal dysfunction are due to small hiatus hernias,‡ it is interesting that no such lesion was found at autopsy.

Although the prognosis in treated cases is usually favorable,[2] death from intercurrent infection may occur.[3] The pathological findings in the present case were similar to those reported previously,[3] calcification in the ejaculatory ducts of the prostate being an additional interesting feature.

A biochemically similar syndrome, including thirst, polyuria, and rickets, with persistent acidosis and nephrocalcinosis, has been reported in adults.[12] In Case 2, there was a history of polydipsia and growth was stunted, but since persistent acidosis and bone changes were absent, it can hardly be in-

* These data have been reported elsewhere.[5]

† References 2 and 8-10.

‡ References 11 and 13.

cluded in this group. The renal functional studies suggested some impairment of glomerular filtration together with decreased ability to concentrate and acidify the urine and excrete ammonia under stress. Tubular sensitiveness to parathyroid hormones and to a carbonic anhydrase inhibitor was preserved.

In this patient the etiology of tetany and the relationship of the clinical and biochemical findings to previously described syndromes is obscure. Since there was no clinical evidence of steatorrhea, it seems probable that hypocalcemia resulted from an excessive loss of calcium in the urine. The normal bone films and Sulkowitch test suggest, however, that this was an acute process, apparently related to infection on both occasions. The renal function studies do not suggest either glomerular or tubular dysfunction sufficient to account for the blood findings, even taking into account the high consumption of cow's milk. Although nephrocalcinosis is not a feature of hypoparathyroidism, it seems possible that disturbed parathyroid function may have been a significant factor in producing this patient's symptoms. His subsequent course will be followed with considerable interest.

SUMMARY

Two further cases of renal tubular disease with nephrocalcinosis are described. In one case, a young infant, profuse hematemesis was an early symptom and was associated with the radiological findings of gastroesophageal incompetence. The disease terminated fatally, with infection, dehydration, and thrombosis of the inferior mesenteric vein. Nephrocalcinosis was demonstrated at autopsy. In the other case, occurring in an older child, the presenting symptom was tetany with hypocalcemia. Nephrocalcinosis was demonstrated radiologically. The nature of the underlying disorder was obscure, and the possible importance of endocrine as well as renal factors in the production of the symptom-complex is discussed.

Dr. F. W. Wiglesworth supplied the pathological report and photomicrographs in Case 1. Dr. Wiglesworth, Dr. Alan Ross, and Dr. Reginald Lightwood gave helpful criticism.

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The Effect of Pancreatin on Fat Digestion in an Infant

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and
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The effectiveness of pancreatin in treatment of pancreatic deficiency has long been a subject of controversy. Recently reported balance studies by Ross [1] and by Harris and co-workers [2] on a total of 23 infants and children indicate that pancreatin is effective in improving fat utilization. Vitamin A absorption studies have also tended to confirm this lipolytic effectiveness of pancreatin.[3]

Additional data regarding the effect of pancreatin on fat digestion are provided by the present study, in which 10 paired balance periods were observed in a single infant with pancreatic exocrine deficiency. The age of the infant was 2 months at the beginning of the experiment. He weighed 4500 gm. at that time and increased to 5400 gm. by the end of the study, at age of 4 months. No family history of pancreatic exocrine disease was known. Pancreatic deficiency was proved by duodenal drainage with use of secretin and double-lumen gastroduodenal tube. One of these tests was performed at the age of 2 months. The volume of fluid aspirated after intravenous injection of secretin was 0.2 ml. in 20 minutes. The fluid was dark yellow and slightly alkaline. The undiluted juice produced no tryptic action on x-ray film in 15 minutes at room temperature. At age of 7 months, the duodenal drainage was repeated. The volume obtained this time was 0.9 ml., and the fluid was alkaline and brown. The trypsin test on x-ray film was again negative. The trypsin concentration, as determined by the modified Anson method, was 0.9 ($\times 10^{-4}$), which is in the range for the extreme degree of pancreatic deficiency in the typical case of cystic fibrosis of the pancreas.* In the normal infant the volume is 1-10 ml. and the trypsin concentration 30-120 ($\times 10^{-4}$). The gastric juice was strongly acidic. The infant had no apparent pulmonary disease, so that confusion of interpretation incident to administration of antibiotics was avoided. There were still no pulmonary symptoms at the time of the later check-up, at age of 7 months. By this time the infant had not been given antibiotics except for two weeks during one respiratory infection, which terminated without residual symptoms. Parotid salivary chloride levels at ages of 2 and 7 months were 99 and 92 mEq. per liter, in comparison with values ranging from 17 to 55 mEq. in nonfibrocystic infants past the newborn period.[6] Sweat tests were done at the ages of 2 months and 7 months. The chloride levels of the sweat were 82 and 100 mEq. per liter, respectively, compared with a normal range of 10-70 mEq.[7]

Ten periods using pancreatin (Viokase powder) were alternated with ten periods using casein (Casec) as a protein control substance. The dosage of pancreatin was 1 gm. with each bottle feeding, five times daily. The feeding consisted essentially of milk, in the form of evaporated milk diluted with an equal part of water, given five times daily. The quantity of milk given was determined by the appetite of the infant, but it

Submitted for publication Jan. 5, 1956.

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This study was aided by the Gary Ralston Memorial Fund and by a grant from the A. M. A. Council on Pharmacy and Chemistry.

* References 4 and 5.

was measured. Ten to twenty grams of Pablum was also given daily.

The test periods were of the duration of three days each. Each period was initiated by a dose of solution of carmine, 1 drop per ounce of formula in the early morning formula. The stool periods were separated according to the marking thus obtained in the stool. To facilitate stool collection, a thin plastic sheet (Saran Wrap) was placed in the diaper. Any stool adhering to the buttocks was added to the material on the plastic sheet. The stools in the sheet were gathered in a refrigerator until completion of a test period. This simple technique proved practical in a general pediatric ward. The accuracy of it may be inferred from the reproducibility of the stool-collection periods.

Fat Balance Studies With and Without Pancreatin

	Control Periods			Pancreatin Periods		
	Wt. of Wet Stool, Gm.	Fat in 100 Gm. Wet Stool, Gm.	Fat Loss in Stool, % of Intake	Wt. of Wet Stool, Gm.	Fat in 100 Gm. Wet Stool, Gm.	Fat Loss in Stool, % of Intake
1	330	14	50	246	15	40
2	298	14	37	190	9	18
3	398	15	62	170	15	28
4	413	19	75	254	14	32
5	430	15	70	196	13	25
6	427	13	42	287	11	24
7	545	14	56	416	14	50
8	468	16	70	326	15	38
9	454	16	61	294	17	26
10	462	16	52	413	13	41

At the end of each stool-collection period, total specimens plus wrappers were weighed, and weight equivalent to the wrappers was subtracted. Most of the stool was scraped from the wrappers and mixed thoroughly by a spatula. Five gram aliquots of the wet mixture were taken for analysis by the method of van de Kamer and co-workers.[8] In this method the wet stool sample was hydrolyzed in alcoholic KOH. The mixture was acidified and chilled. A definite volume of petroleum ether was then added. An aliquot of the petroleum ether was titrated with isobutyl alcoholic KOH, using thymol blue as indicator.

The results are shown in the accompanying Table. The amount of fat appearing in the stool in the 10 control periods varied from 37% to 75% of the fat ingested; the mean was 58%, and the standard deviation, 13%. In the 10 alternating pancreatin periods, the fat excretion varied from 18% to 50% of the fat ingested and the mean was 33%, with standard deviation 9%. A slight overlapping of the groups is thus seen. The difference between the two means is more than five times the standard error of the difference; consequently, the results are highly significant. There was little change in the consistency of the stool or its concentration of fat with or without pancreatin. The calculated increase in fat utilization with pancreatin depended on the decreased total weight of stool.

SUMMARY

Ten pairs of fat balance studies were done between the ages of 2 and 4 months on an infant with pancreatic deficiency receiving a whole-milk formula. Fat wastage decreased from 58% of the intake to 33% when high potency pancreatin was used in dosage of 1 gm. with each milk feeding, five times daily.

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Subdural Hematoma in Infancy

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Subdural hematoma in infancy is indeed a well-known clinical entity, and equally well known is the multiplicity of signs and symptoms of this condition and their lack of specificity, which add to the difficulty of the clinical diagnosis. Consequently, there is frequently a delay in the diagnosis which may be the cause of the poor results of surgical intervention, the damage to the brain being irreversible. Furthermore, groups of cases described by various authors, although having many points in common, may differ in the kind and frequency of various manifestations.

In studying our material, consisting of 19 cases, we hoped to determine, by analyzing the history and clinical features, whether an earlier diagnosis on our part would be possible. We attempted to evaluate the result of treatment by correlating the child's postoperative development with the findings at the time of operation.

CLINICAL FEATURES

Of the 19 cases reviewed here, 12 are boys and 7 girls. These figures are too low to draw any conclusions from them, but it is nevertheless noteworthy that a similar preponderance of boys has been reported by other authors.*

The age of the children on admission to the hospital is shown in Chart 1. In all these cases except one, the symptoms appeared during the first nine months of life. More than 50% of children were admitted to the hospital between the ages of 4 and 6 months.

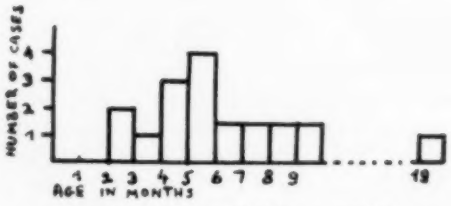


Chart 1.—Age at admission to hospital.

The frequency of various signs and symptoms in our series of cases is presented in Chart 2. In 14 out of 19 children the head circumference was much larger than normal for their age, and in most cases the enlargement of the bitemporal diameter was especially noticeable. In the series of most of the other authors head enlargement was not observed in such a high percentage.† This could be explained by the fact that most of the cases in this series were brought to our attention in the early days because of this particular sign, and many others with less outstanding features were probably not even brought to our notice. With more widespread knowledge of this condition, more cases have been diagnosed in which head enlargement was not present to an appreciable degree.

†References 1 and 3.

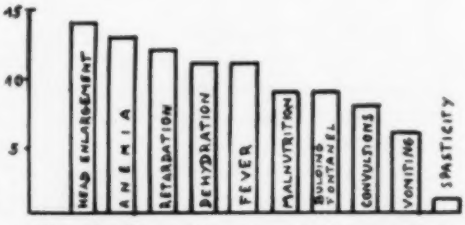


Chart 2.—Signs and symptoms in 19 cases of subdural hematoma in infancy.

Submitted for publication Jan. 8, 1956.

From the Department of Pediatrics and the Department of Neurosurgery, Hadassah Hebrew University Hospital.

* References 1 and 2.

ETIOLOGY

For many years trauma was thought to be the most important, if not the only, etiological factor in subdural hematoma.‡ Ingraham and Matson § stressed the fact that trauma may be very slight, and this led to the assumption that if subdural hematoma was found preceding trauma had occurred.

The pathogenesis of subdural hematoma is described in many excellent papers and will not be repeated here. In our series of cases a history of trauma was elicited in two cases only, two others having a history of difficult delivery.

In 1950, McKay, Morissette, Ingraham, and Matson [5] called attention to the occurrence of xanthochromic fluid in the subdural space in some cases of Hemophilus influenzae meningitis. Independently, Smith, Dormont, and Prather [6] reported 20 cases with subdural effusion complicating meningitis due to various bacteria. Many other clinical reports followed these preliminary descriptions.‖ The mechanism is not clearly understood, although it seems probable that an effusion takes place through the irritated or damaged capillary wall.¶

In four of our cases the clinical findings on admission to hospital established the diagnosis of meningitis. The organisms found were Diplococcus pneumoniae in two cases and H. influenzae in one case, and in the fourth case the causative agent could not be identified. After an interval of 5 to 20 days a subdural hematoma was discovered, and on operation thick membranes with brain atrophy were found. It was our impression, therefore, that the subdural hematoma preceded the meningitis. In one of the cases pneumococci were found in smears taken from the subdural fluid as well as in the culture from the spinal fluid. We assumed, therefore, that we were dealing in these cases with a subdural hematoma which had become infected and with a secondary spreading of the infection into the subarachnoid space.

Among other etiological factors of subdural hematoma in infancy, diarrhea with dehydration and severe malnutrition has recently been mentioned in the literature,[9] but it was stressed long ago that subdural hematoma occurs with greater frequency in malnourished children.[11] Four patients in our series suffered from severe diarrhea with dehydration before the occurrence of other signs of subdural hematoma. In these cases it seems difficult to determine the sequence of events. While the subdural hematoma may in some cases occur in infants with diarrhea and malnutrition, these latter conditions may be the first clinical sign of a subdural hematoma. The pathogenesis of subdural hematoma following diarrhea is not clearly understood, because our knowledge of the various disturbances here is still incomplete. It seems to us, however, that a decrease of plasma prothrombin in infantile diarrhea, as found by Matoth,[12] may be of importance in the pathogenesis of this condition.

One of our children suffered from a severe undiagnosed bleeding disorder which was, most probably, the cause of the subdural hematoma in this particular case. It is of interest that there is no evidence in the literature that hemorrhagic diseases play much of a part in the etiology of this condition.[2] We are inclined to favor the view that interference with blood coagulation, which is known to be frequent in many states in infancy, is a very important contributing factor in the pathogenesis of subdural hematoma.

In two cases of suspected subdural hematoma the first subdural tap was negative, while the second, at an interval of three weeks, showed yellow fluid in the subdural space. It seems to us that there is a possibility of bleeding during a diagnostic subdural tap, especially in infants with a subclinical bleeding tendency. The possibility of a subsequent development of a subdural hematoma after this procedure should be considered. For greater safety, we believe

‡ References 3 and 4.

§ References 1 and 4.

‖ References 2 and 7-9.

¶ References 8 and 10.

that it is not superfluous to determine the bleeding and coagulation time in the infant prior to performing a subdural tap.

DIAGNOSIS

The diagnosis was confirmed in our cases by subdural taps, which disclosed bloody or xanthochromic fluid. In two cases with closed fontanels burr holes were made.

In 11 children an electroencephalogram was done prior to the operation. All these children had markedly abnormal EEG's. The abnormalities were regional reduction of voltage, areas of slow-wave activity, or a combination of both. The literature on electroencephalogram in subdural hematoma is very limited.# The findings were not conclusive, and therefore the EEG is believed to be of little help in the diagnosis. However, it seems to us that our findings were of some value. In an entity in which the diagnosis has to be made on nonspecific signs and symptoms, a normal EEG may rule out the need for an immediate subdural tap, while an abnormal EEG may supply additional weight in favor of the performance of this procedure.

OPERATIVE STATISTICS

Of 19 cases, 2 children died before surgery could be undertaken, 1 of a complication after mastoidectomy, the other of a severe bleeding disorder in which the risk of surgical intervention was too great. Seventeen children underwent operation, in two of them only burr holes were made, without removal of the membranes of the hematoma. In one of these two children the membranes were thick and the underlying brain was severely atrophic; in the other the membranes were too thin to be removed.

Fifteen cases were treated according to the procedure described by Ingraham and Matson.* After repeated subdural taps in order to decrease the intracranial pressure gradually, exploratory burr holes were made to establish the presence of membranes, and craniotomy was performed with wide excisions of both inner and outer membranes of the hematoma.

In 3 cases the hematoma was unilateral; in the remaining 16 cases, bilateral. Three children died of respiratory and cardiac arrest during operation. These cases were among the earlier ones, before proper anesthetic technique was established here, a vital factor in neurosurgery in infancy. One child died a week after the operation with a severe local infection and extreme brain atrophy.

FOLLOW-UP

Ten children with membrane removal were restudied after a time interval ranging from six months to six years. The studies included anamnesis, with special attention to the child's physical and mental development and possible neurologic manifestations, complete physical examination, and in most cases electroencephalogram and pneumoencephalogram studies. The psychomotor development was satisfactory in four children, including our first patient, who was reexamined six years after the operation. In four other children the development was moderately retarded, and two children were severely mentally deficient. Each of these severely deficient children had had an infected subdural hematoma. One child suffered from recurrent convulsive seizures after the operation in spite of anticonvulsive treatment.

The most outstanding fact was the close relationship between the child's postoperative development and the expansion of the brain at the time of operation, after removal of the membranes. In most of the children developing satisfactorily the brain at the time of operation expanded immediately after the membranes were removed. On the other hand, in those children who remained retarded the brain did not expand and remained atrophic (Chart 3).

The EEG findings showed great improvement after the operation. In eight children the EEG was normal or revealed only slight abnormalities at the follow-up examination.

References 13 and 14.

* References 1 and 4.

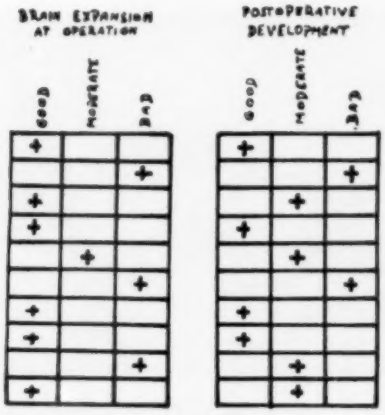


Chart 3.—The correlation between the findings at the time of operation (expansion of the brain) and the child's postoperative development.

However, it has to be taken into account that the children were much older at the follow-up examination, and it is therefore not easy to compare the preoperative and postoperative EEG findings.

Pneumoencephalogram was performed in eight children. The four children with a normal postoperative development and three children out of the four who were moderately retarded had completely normal pneumoencephalograms. The ventricular system was normal in size and shape, and there was a normal amount of air in the subarachnoid space (Fig. 1). The PEG in one child who was moderately retarded after the operation showed a mild enlargement of the entire ventricular system. Unfortunately, no PEG could be obtained in the two children severely retarded after the operation.

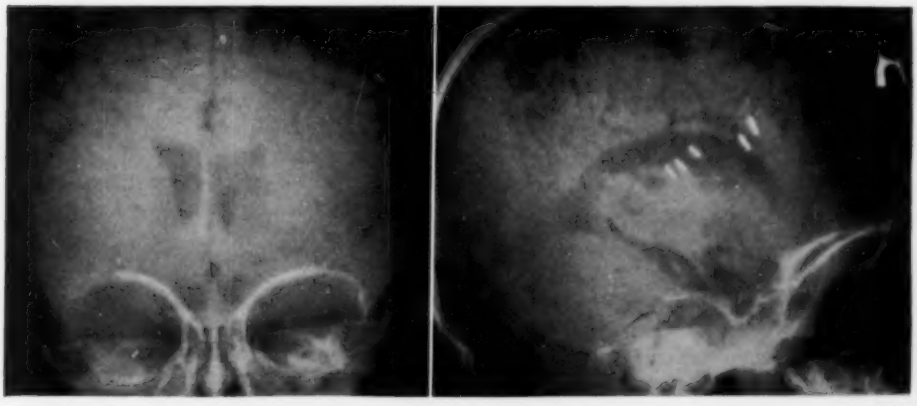
The child in whom the membranes were not removed because of the existing brain atrophy was also reexamined one year after the first admission. He was moderately retarded, and the PEG revealed a hydrocephalus (Fig. 2). This was most probably a hydrocephalus ex vacuo due to the severe brain atrophy.

SUMMARY AND CONCLUSIONS

In analyzing a series of 19 cases of subdural hematoma in infancy, we found the most outstanding sign to be enlargement of the head, particularly in the bitemporal diameter. In 14 of the 19 cases suspicion of intracranial pathology was aroused because of this sign.

We were not able to confirm the findings of subdural effusion as a result of meningitis. In the four cases having both meningitis and xanthochromic fluid in the subdural space, no definite conclusion could be drawn as to which of the two lesions preceded the other. Our impression was that all these four cases had a subdural hematoma antedating the meningitis. The thick and old membranes, found at the operation, spoke for this conclu-

Fig. 1.—A normal pneumoencephalogram in one case of subdural hematoma in infancy 15 months after operation.



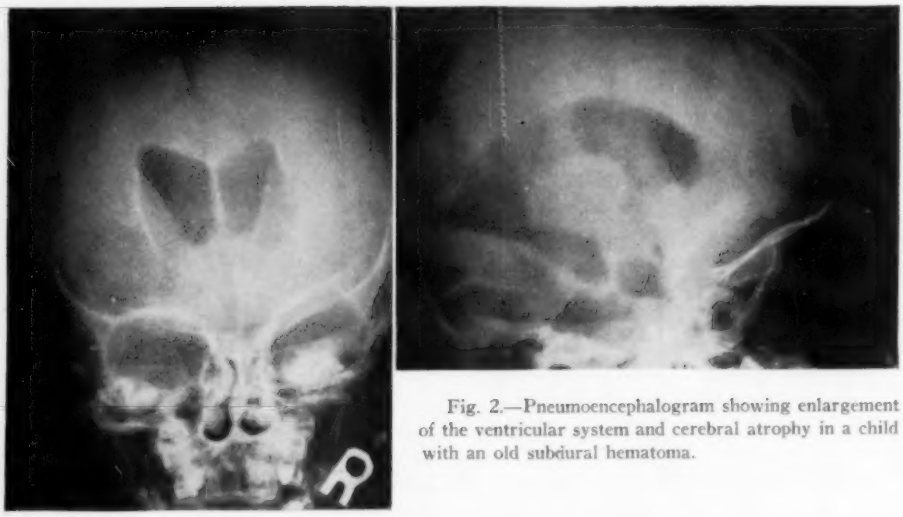


Fig. 2.—Pneumoencephalogram showing enlargement of the ventricular system and cerebral atrophy in a child with an old subdural hematoma.

sion. In one case we found a common infection in the subdural space and the leptomeninges.

In children with dehydration and malnutrition we think it is extremely difficult to decide whether these states are the cause or the result of the subdural hematoma; the sequence of events in these conditions is still obscure. It seems to us that iatrogenic subdural hematoma may exist. The diagnostic subdural tap may possibly cause a hematoma in some cases, especially in children with a clinical or subclinical bleeding tendency.

An early diagnosis of this condition is desirable, but the means of an early diagnosis are still absent. As all 11 cases in which an EEG was performed showed markedly abnormal records, it seems to us that EEG may be of assistance in supporting a clinical suspicion of intracranial pathology and therefore also of subdural hematoma. An abnormal EEG should therefore contribute to the indications for a diagnostic tap.

We found a definite correlation between the development of the children after the operation and the findings at the operative table. Satisfactory psychomotor development has been obtained in children in whom the brain had expanded after the membranes of the hematoma had been removed. It seems of interest to note that hydrocephalus, probably ex vacuo, may be a sequel of an old subdural hematoma, as shown by one of our cases.

Dr. M. Streifler, of the Neurological Department of the Hadassah Hebrew University Hospital, explained the electroencephalographic findings. Dr. S. Levin, Tiberias, referred two cases to our hospital.

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Pulmonary Lesions in Experimental Oxygen Poisoning

Studies with I^{131}-Labeled γ-Globulin and Albumin

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and
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With the Technical Assistance of Vera E. Drose, Aaron J. Blumberg, and Warren E. Cooper

Recently there has been increasing awareness that deaths of premature infants are frequently associated with the presence of hyaline-like membranes in the lungs. Bruns and Shields [1] have confirmed the finding of Pichotka and Kühn [2] in guinea pigs made to breathe high concentrations of oxygen, namely, the development of a hyaline-like membrane in the lungs which bears a striking resemblance to that found in premature infants. These studies have suggested that this histologic picture may be produced by the precipitation of material of endogenous origin, perhaps protein, rather than the inhalation of exogenous material, such as amniotic fluid.

The possibility that endogenous protein contributes to the pathogenesis of the pulmonary lesion can be most expeditiously explored by the use of isotopically labeled protein fractions. The purpose of the present study, employing I^{131}-tagged protein fractions, γ-globulin and albumin, was to determine the role of these substances, as well as electrolytes and water, in the pathogenesis of the pulmonary lesions induced in guinea pigs by exposure to a high concentration of oxygen at normal atmospheric pressure.

Submitted for publication Jan. 23, 1956.

From the Departments of Medicine and Obstetrics and Gynecology, University of Colorado School of Medicine. Established Investigator of the American Heart Association (Dr. Aikawa).

This work was supported in part by a grant-in-aid from the American Heart Association and in part under a contract with the United States Atomic Energy Commission.

MATERIAL AND METHODS

Forty guinea pigs of both sexes, weighing between 200 and 250 gm., were employed.

Purified fractions of human plasma—γ-globulin and albumin *—were labeled with tracer amounts of I^{131}, stored in a refrigerator until use, and diluted with sterile physiologic saline solution immediately prior to injection into animals.

All radioactivity assays were made with a Nuclear Model DS-3 well-type scintillation counter, which was attached to a Tracerlab Superscaler. All counting rates were corrected for physical decay.

Flame photometry, for sodium and potassium determinations, was performed with a Barclay internal standard instrument.

A specially constructed all-plastic oxygen chamber was used to expose guinea pigs to 98% oxygen at a pressure of 760 mm. of mercury.

EXPERIMENT 1.—Twenty animals were used in the study with I^{131}-labeled human γ-globulin. Each of 10 guinea pigs was given an intravenous injection of 2.5μc of radioactivity, contained in 0.875 mg. of human γ-globulin in 0.25 ml. of physiologic saline solution. The other 10 animals were not given injections and served as controls. Five of the guinea pigs which were given injections (Group A) and five which were not (Group B) were placed in the oxygen chamber and exposed to 98% oxygen at a pressure of 760 mm. of mercury.

* I^{131}-tagged γ-globulin and albumin were obtained from Abbott Laboratories, North Chicago, Ill., and Oak Ridge, Tenn., on authorization from the U. S. Atomic Energy Commission.

Temperature and humidity were not rigidly controlled, but remained in the neighborhood of 25 C and 50%, respectively. The animals were kept in the oxygen chamber until death occurred spontaneously. The remaining five guinea pigs which had been given injections (Group C) and five which had not (Group D) were left outside the oxygen chamber in the same room at the usual atmospheric conditions. All animals were provided with food and water.

EXPERIMENT 2.—Twenty animals were used in this study. Ten were given intravenous injections of 10μc of radioactively as I^{131}-tagged human serum albumin in 0.25 ml. of physiologic saline solution, and the remaining 10 were not given injections and served as controls. Thus, five animals (Group A) were given injections of albumin and placed in the oxygen chamber; five (Group C) were given injections and left at usual atmospheric conditions; five animals which were not given injections (Group B) were placed in oxygen, and the remaining five (Group D) were not given injections and were left in air.

When an animal in the oxygen chamber died spontaneously, it was removed, and another animal in the corresponding control group in air was killed by a blow to the head at approximately the same time interval. Both were subjected to autopsy, and the lungs were removed and stored in a frozen state until further analyses were performed. The total lung weights were determined, and three samples of lung tissue from each guinea pig, each sample weighing approximately 1 gm., were placed in previously weighed test tubes. After a radioactivity assay was made, the test tubes were heated at 110 C for at least 18 hours in a drying oven to constant weight in order to determine the total water content. The dried residue was then soaked for at least 72 hours in a known volume of distilled water. The supernatant fluid, after centrifugation, was used for determining the sodium and potassium concentrations of the tissues.

Statistical Analysis.—The significance of the difference between the means was derived by the use of the *t*-test.[3]

RESULTS

EXPERIMENT 1 (Table 1 and Fig. 1).—The mean period of survival in the animals given injections of tagged γ-globulin and exposed to 98% oxygen (Group A) was 64 hours, as compared with a mean of 75 hours in Group B, the animals which were not given injections and which were placed in oxygen; this difference in survival time, however, was not significant. Those animals which were not in the oxygen chamber, whether previously given injections of γ-globulin (Group C) or not (Group D), were killed at approximately 80 hours.

The weight and water content of the lungs were significantly greater in the animals exposed to oxygen (Groups A and B) than in those not so treated (Groups C and D). There was no significant difference in the weight and water content of the lungs between the animals in oxygen given injections of γ-globulin (Group A) and those not given injections (Group B).

Both the concentration and the total content of radioactivity in the lungs were significantly greater in Group A than the mean values obtained in Group C.

When expressed in relation to the volume of tissue water or the wet weight of tissue, the mean concentration of sodium in the lungs of animlas in Group A was not significantly different from the respective mean values obtained in Group C. However, when tissue sodium concentration was expressed in relation to the dry weight of tissue, the mean value in Group A was nearly twice as high as that in Group C and approached a significant difference.

The mean tissue concentration of potassium in Group A, when expressed in relation to the volume of tissue water, was about one-half the mean value found in Group C, although this difference was of borderline significance. No significant difference in the mean value for potassium per kilogram of dry weight of tissue was found between the two groups.

EXPERIMENT 2 (Table 2 and Fig. 2).—The mean survival time for those animals given injections of tagged albumin and exposed to 98% oxygen (Group A) was 75 hours, compared with a mean of 96 hours in those animals not given injections but placed in oxygen (Group B). This difference, however, was not significant. Comparison of the animals in oxygen (Group A) with those in air (Group C) revealed that the lungs of the former were significantly higher in weight, water content, and radioactivity concentra-

TABLE 1.—*Summary of Results: Experiment 1. Guinea Pigs Given Intravenous Injections of I^{131}-Labeled Human γ-Globulin*

	Group A, Injection and in Oxygen	Group B, No Injection and in Oxygen	Group C, Injection and in Air	Group D, No Injection and in Air
Time of death (hr.)	64	75	80	80
Total lung weights (gm.)	10.4±0.44*	8.9±0.59	4.1±0.48	3.6±0.15
Water content (% wet wt.)	87.3±0.67	86.4±0.51	80.8±0.96	80.0±0.83
Radioactivity				
(cpm/gm. wet wt.)	15,588±1,400	.....	6,221±1,000	.....
(cpm/total wet wt.)	161,450±12,000	.....	27,064±8,000	.....
Tissue sodium				
(eonc/liter tissue water)	109.1±2.62	.....	97.2±4.02	.....
(conc/kg. wet wt.)	96.0±2.94	.....	78.7±4.25	.....
(conc/kg. dry wt.)	816.0±73.2	.....	418.9±49.6	.....
Tissue potassium				
(conc/liter tissue water)	44.5±5.00	.....	79.7±6.68	.....
(conc/kg. wet wt.)	38.9±4.07	.....	64.1±4.74	.....
(conc/kg. dry wt.)	320.4±16.3	.....	331.5±9.6	.....

Measurements	Groups Compared	$\bar{d}$	$s\bar{d}$	t
Total lung weight	A vs. B	1.5†	0.74	2.03
	A vs. C	6.3	0.65	9.69‡
	A vs. D	6.8	0.47	14.51‡
	A+B vs. C+D	5.8	0.50	11.61‡
Water contents (% weight)	A vs. B	0.09	0.09	1.00
	A vs. C	0.65	0.12	5.41‡
	A vs. D	0.73	0.11	6.64‡
	A+B vs. C+D	0.65	0.11	5.90‡
Radioactivity				
(cpm/gm. wet wt.)	A vs. C	0.98	0.17	5.76‡
(cpm/total wet wt.)	A vs. C	13.4	1.50	8.93‡
Tissue sodium				
(conc/liter tissue water)	A vs. C	1.19	0.48	2.48
(conc/kg. wet wt.)	A vs. C	1.73	0.52	3.33
(conc/kg. dry wt.)	A vs. C	3.97	0.89	4.46
Tissue potassium				
(conc/liter tissue water)	A vs. C	3.52	0.83	4.24
(conc/kg. dry wt.)	A vs. C	0.11	0.19	0.58
(conc/kg. wet wt.)	A vs. C	2.51	0.63	3.98

* Mean ± standard error.
† Coded values.
‡ Statistically significant difference; P = less than 0.01.

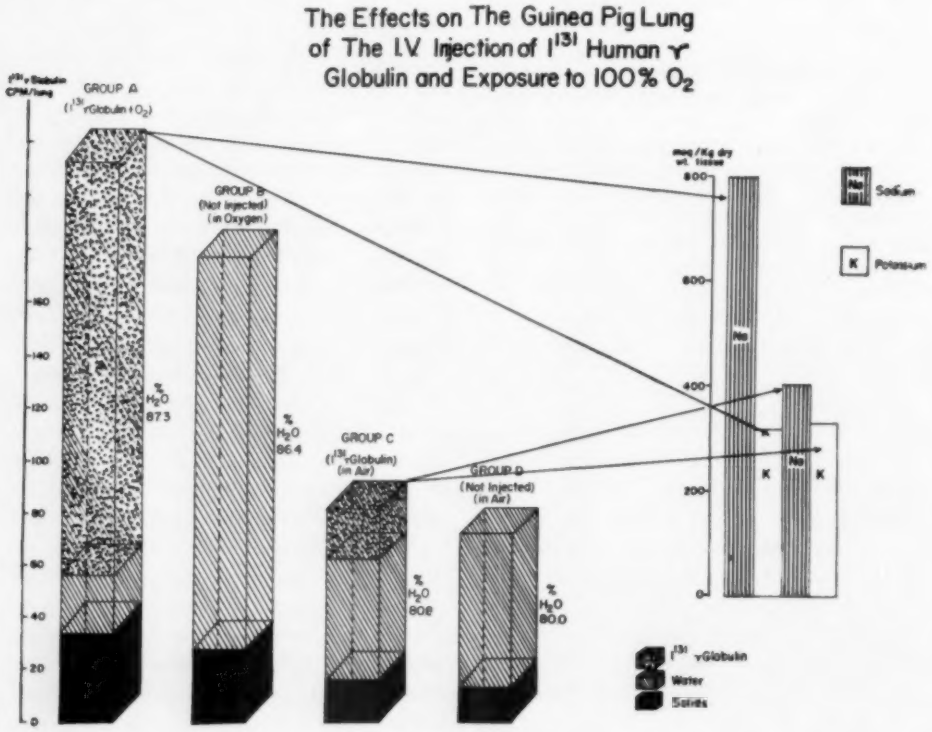


Figure 1

TABLE 2.—*Summary of Results: Experiment 2. Guinea Pigs Given Intravenous Injections of I^{131}-Labeled Human Serum Albumin*

	Group A, Injection and in Oxygen	Group B, No Injection and in Oxygen	Group C, Injection and in Air	Group D, No Injection and in Air
Time of death (hr.)	75	96	80	80
Total lung weights (gm.)	9.2±0.54*	8.8±0.58	2.9±0.13	3.0±0.39
Water content (% wet wt.)	87.44±0.50	87.90±0.33	81.33±0.40	80.95±0.10
Radioactivity				
(cpm/gm. wet wt.)	53,048±7,960	.....	30,199±5,220	.....
(cpm/total wet wt.)	489,839±79,000	.....	87,860±15,500	.....
Tissue sodium				
(conc/liter tissue water)	106.6±2.1	.....	77.4±2.9	.....
(conc/kg. wet wt.)	93.3±2.9	.....	63.2±2.6	.....
(conc/kg. dry wt.)	750.6±43.0	.....	345.5±19.6	.....
Tissue potassium				
(conc/liter tissue water)	45.8±1.04	.....	92.3±1.14	.....
(conc/kg. wet wt.)	40.0±2.7	.....	75.4±2.9	.....
(conc/kg. dry wt.)	318.9±13.4	.....	410.8±17.0	.....

Measurements	Groups Compared	$\overline{d}$	$s_{\overline{d}}$	t
Total lung weight	A vs. B	0.44†	0.80	0.55
	A vs. C	6.34	0.56	11.32‡
	A vs. D	6.24	0.67	9.32‡
	A+B vs. C+D	6.07	0.54	11.24‡
Water contents (% weight)	A vs. B	0.04	0.06	0.77
	A vs. C	0.61	0.063	9.70‡
	A vs. D	0.65	0.05	12.73‡
	A+B vs. C+D	0.653	0.035	18.66‡
Radioactivity				
(cpm/gm. wet wt.)	A vs. C	2.28	0.95	2.40
(cpm/total wet wt.)	A vs. C	4.02	0.81	4.90‡
Tissue sodium				
(conc/liter tissue water)	A vs. C	2.92	0.36	8.09‡
(conc/kg. wet wt.)	A vs. C	3.01	0.39	7.72‡
(conc/kg. dry wt.)	A vs. C	4.05	0.47	8.62‡
Tissue potassium				
(conc/liter tissue water)	A vs. C	4.65	0.49	9.50‡
(conc/kg. dry wt.)	A vs. C	0.92	0.22	4.24
(conc/kg. wet wt.)	A vs. C	3.54	0.40	8.94‡

* Mean ± standard error.
† Coded values.
‡ Statistically significant difference; P = less than 0.01.

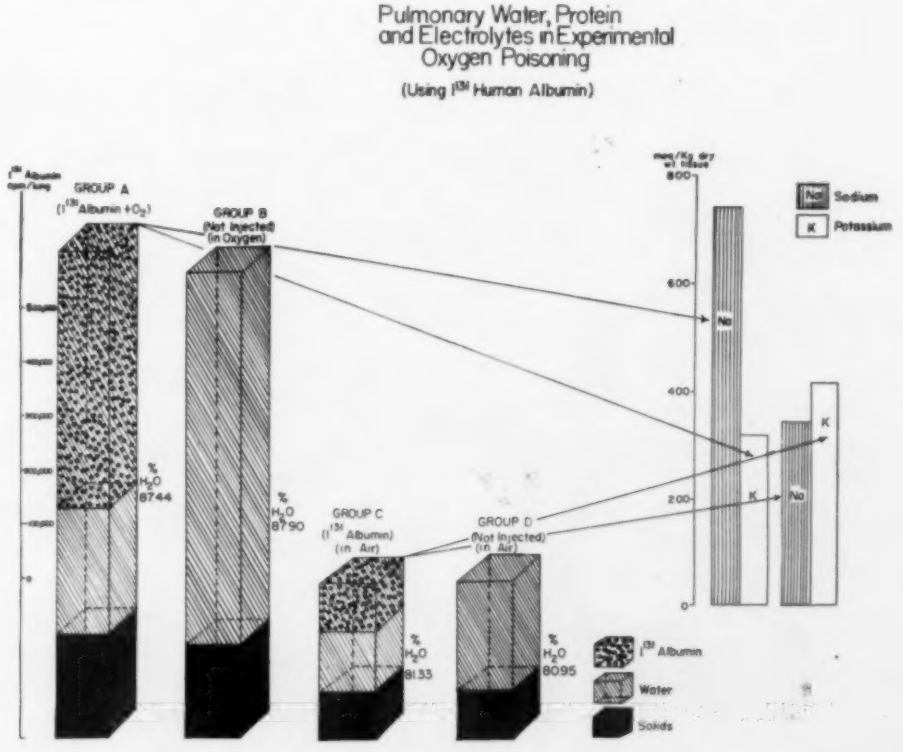


Figure 2

tion and content. The relative magnitudes of these differences between Groups A and C were practically identical with those noted in Experiment 1.

In those guinea pigs given injections of iodinated albumin, the tissue potassium concentration was suggestively or significantly lower in the animals exposed to oxygen (Group A) than in the control animals (Group C), in spite of the increase in lung weight and water content in the former.

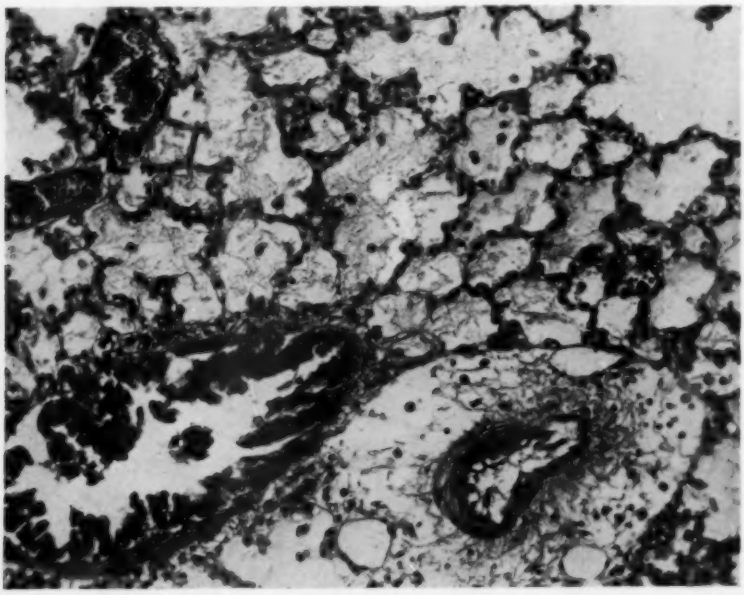
COMMENT

Previous studies on the pathogenesis of oxygen poisoning in animals and of the disease which produces hyaline-like membranes in the lungs of newborn infants have been concerned primarily with qualitative histopathologic descriptions.[4] In all of those studies, lungs have been described grossly as "liver-like," exuding a frothy material on cut section, and sinking when placed in water or formalin. Microscopically the predominant picture is that of edema, which is usually perivascular, together with congestion, hemorrhage, epithelial degeneration, and the presence occasionally of a hyaline-like membrane.

In the present experiment, the lungs of all the animals exposed to oxygen showed the histologic findings usually associated with oxygen poisoning (Fig. 3). The histologic picture did not appear to be altered by the injection of tagged purified plasma fractions.

Although it was recognized that the ideal substances for use in the present study were homologous globulin and albumin labeled with I^{131}, it was not possible to iodinate fractions of plasma from guinea pigs. It was recognized that the injection of heterologous antigenic protein substances might result in sensitization, with the resultant production of antibody. Humoral antibodies usually do not appear until seven to nine days after the injection of antigen,[5] however, and all of the animals in oxygen were dead within four days. It therefore appears improbable that hypersensitivity played a role in the production of the pulmonary lesions. Moreover, the histologic picture and composition of the

Fig. 3.—Microscopic section of a lung of a guinea pig exposed to 98% oxygen at 760 mm. of mercury. Death occurred at 64 hours. Note the predominant perivascular and intra-alveolar edema.



lungs were similar in all animals exposed to oxygen, whether or not the tagged material was injected before exposure. Since previous studies have shown that iodinated protein fractions retain their radioactive tag as long as the protein molecule remains intact,[6] it has been assumed that the distribution and concentration of the radioactivity are indicative of the behavior of the entire labeled protein molecule and that changes in the distribution of the labeled material reflect changes in the distribution of the native guinea pig protein fractions.

There have to date been very few studies on oxygen poisoning which report measurements of the changes in composition of the lung. Although the weight of the lungs under these experimental conditions has been reported, only Hemingway and Williams [7] have measured the amount of pulmonary edema present. In their study on guinea pigs exposed to 95% to 99% oxygen, the lungs approximately doubled in weight and in the content of soluble protein nitrogen, which was used as an index of plasma protein. The pulmonary hemoglobin did not increase significantly.

The present study offers additional evidence to suggest that the increase in lung weight occurring as a result of oxygen poisoning is due, at least in part, to an excessive accumulation of sodium, water, albumin, and γ-globulin. It is not known whether a protein fraction with a molecular weight higher than γ-globulin, such as fibrinogen, also contributes to the pulmonary edema.†

Normally, most of the potassium in the body is located intracellularly. It will be recalled that in both the present experiments the concentration of potassium, when expressed in relation to the dry weight of tissue, did not differ significantly in Groups A and C. This finding suggests that the increase in lung weight was not due to an increase in the amount of pulmonary parenchyma. The experimental results are most compatible with the interpretation that cellular mass remained constant, or even decreased, and that the increase in lung weight was due principally to an extravascular, interstitial accumulation of sodium, water, and plasma proteins resulting from a localized increase in capillary permeability.

Inference.—Recently, there has been considerable discussion concerning the possible relation of retrolental fibroplasia to pulmonary hyaline membranes in the premature infant.† It is well established clinically and experimentally that hyperoxia is the probable cause of retrolental fibroplasia in the newborn infant. No such clear-cut evidence is available concerning the pathogenesis of pulmonary hyaline membranes in the premature infant. The results of the present experiment leave little doubt that hyperoxia will damage the pulmonary capillaries sufficiently to permit the abnormal leakage of noncellular blood elements. When this capillary injury in the guinea pig becomes extensive, the animal usually dies of pulmonary edema. The exact role played by the hyaline membranes found in these animals' lungs has not been ascertained. Neither has the role of hyaline membranes in the death of premature infants been established. Perhaps the underlying pathology in both clinical and experimental "hyaline membrane disease" may be increased capillary permeability, with the "membranes" only incidental findings. If this assumption is correct, the two disease processes in the premature infant—namely, retrolental fibroplasia and "hyaline membrane disease"—are both essentially due to capillary injury, which is in part related to hyperoxia, and are thus closely allied in pathogenesis.

SUMMARY

Guinea pigs were given intravenous injections of tracer amounts of I^{131}-tagged γ-glob-

† Since this article was submitted for publication, Gitlin and Craig (*Pediatrics* **17**:64, 1956) have shown by fluorescein-tagged antibody technique that hyaline membranes are composed of fibrin. Also, Van Breeman and Neustein, at the University of Colorado (personal communication), have demonstrated by electronmicroscopy that hyaline membranes are made up largely of fibrin.

† Reference 8. Eastman, N. J.: Editorial comment on Reference 8.

ulin and albumin and were then exposed to 98% oxygen at 760 mm. of mercury until they died. The lungs were then examined histologically and were analyzed for total weight and for water, electrolyte, and radioactivity content. Control groups consisted of animals given injections of tagged protein and left in normal atmosphere and of animals not given injections and placed in oxygen or left in air.

All animals placed in oxygen, whether they had received injections of γ-globulin or albumin or no injections at all, showed pulmonary lesions characteristic of oxygen poisoning.

The lungs of all animals placed in oxygen, when compared with those of guinea pigs left in air, showed significantly higher mean values for total weight, for water and sodium content, and for concentration and content of radioactivity. The potassium content was not significantly altered.

The results suggest that the increase in lung weight is due to a local accumulation of water, sodium, and plasma proteins. The basic abnormal physiologic process appears to be a localized increase in permeability of capillary membrane to noncellular constituents of the vascular compartment.

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Case Reports

CONGENITAL AORTIC STENOSIS ASSOCIATED WITH ENDOCARDIAL SCLEROSIS

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EARLY in 1954, DuShane and Edwards [1] reported two examples of the relatively uncommon combination of congenital aortic stenosis and endocardial sclerosis of the left ventricle. They expressed the belief that, when the diagnosis is made, surgical correction of the stenotic valve should be attempted. They further cautioned, however, that relief of the stenosis may not in itself be sufficient to restore normal cardiac function. Since no surgical attempt has thus far been reported, it seems desirable to present observations recently made in a patient with this type of condition. This case differs from those reported by DuShane and Edwards,[1] however, in that the endocardial sclerosis involved the left atrium, the left ventricle, and to a slight extent the mitral valve. The aortic stenosis was probably a part of the process of endocardial sclerosis.

REPORT OF CASE

A 5-week-old girl was first seen with the chief complaint of rapid respirations of one week's duration. The patient was the product of an uneventful pregnancy and was delivered spontaneously three weeks prior to term, the birth weight being 2265 gm. Both parents and one sibling were living and apparently in good health. The neonatal period was uneventful, and at 4 weeks of age her weight had increased to 3084 gm. It was at the age of one month that the parents first noticed that the respirations had become rapid. The patient was hospitalized and digitalized for heart failure. She was discharged on June 7, 1955, and on that date was referred for further investigation.

Examination disclosed a rather pale and poorly nourished infant weighing 2814 gm. The respirations were somewhat labored, and the rate was 62 per minute. There was a Grade 4 systolic murmur over the entire precordium, the point of maximum intensity being over the aortic area. The murmur was transmitted to the axilla and to both sides of the neck. The aortic and pulmonic second sounds were not audible. Roentgenographic and electrocardiographic studies indicated left ventricular enlargement (Figs. 1 and 2). A tentative diagnosis of aortic or subaortic stenosis was made, and the infant was hospitalized for further observation and study. Because of the absent second aortic sound it was felt that the patient probably had aortic rather than subaortic stenosis. Surgery was considered but was deferred because the infant improved rapidly. However, on the morning of June 13, because of increasing signs of left ventricular failure, she was scheduled for emergency surgery.

The operation was performed by Dr. William P. Longmire. A bilateral thoracotomy through the fourth interspace revealed the enlarged heart. A distinct thrill was felt in the proximal part of the aorta, indicating a valvular stenosis. While the superior vena cava was being mobilized, the heart action suddenly became poor. The pericardium was quickly opened, and a purse-string suture was placed in the lateral wall of the left ventricle. A small Brock valvulatome was inserted through the ventricle and through the valve. The valvulatome passed rather readily, although there was a slight give on its first insertion. Subsequently the valvulatome passed back and forth easily through the valvular area. The cardiac action following this procedure was very poor, although at one time a regular cardiac beat could be restored and on palpation of the aorta a thrill could no longer be felt. The pericardium was closed with interrupted nonabsorbable surgical (silk) sutures, and the thoracic cage was about to be closed when ventricular fibrillation suddenly ensued. The pericardium was again opened, and the heart was shocked and cardiac massage instituted. However, normal cardiac action could not be restored, and the child was pronounced dead.

Pathologic Findings.—The significant changes were limited to the heart. It was preserved with the lungs as a single specimen and together they weighed 120 gm., which was approximately twice the normal weight for an infant this size. The heart was markedly enlarged, particularly on the left side. On gross inspection, the right auricle was not remarkable except for a patent foramen ovale, which

Received for publication Nov. 17, 1955.

From the Children's Medical Group and the Department of Pediatrics, School of Medicine, University of California.

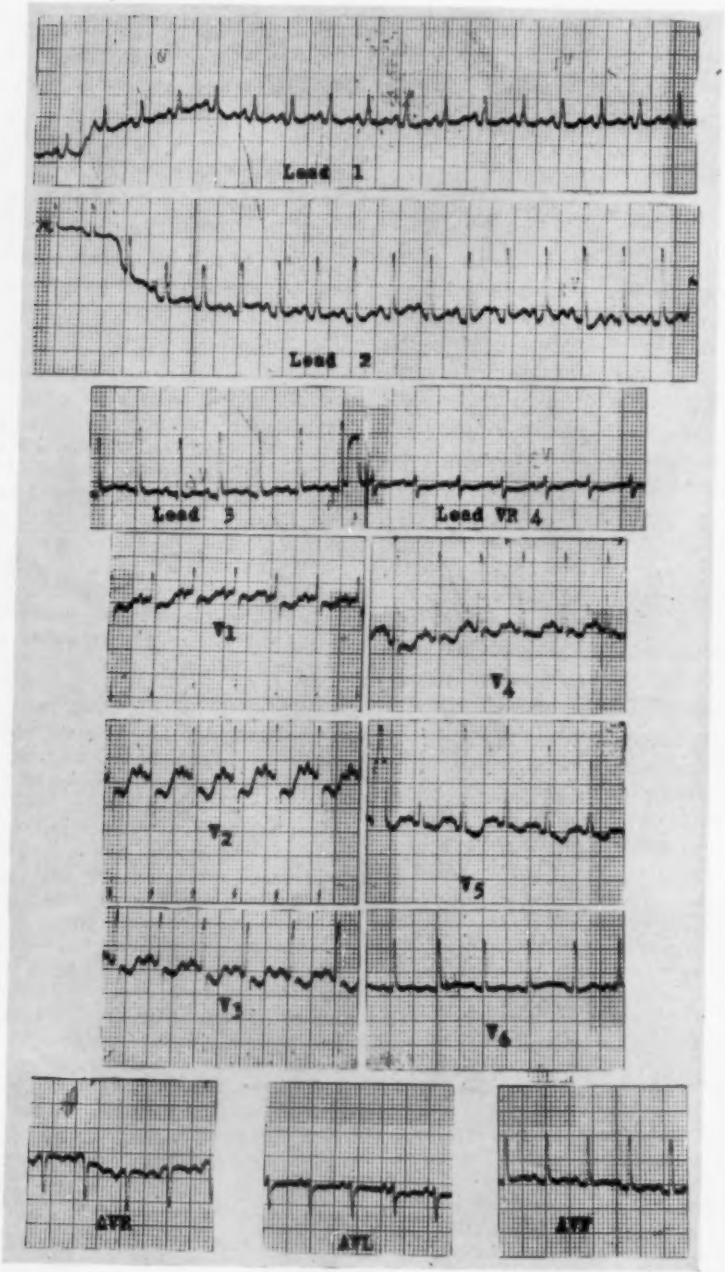

Fig. 1.—Electrocardiogram suggesting left ventricular hypertrophy and associated myocardial changes. The latter could be secondary to digitalis effect, coronary insufficiency, or left ventricular enlargement.

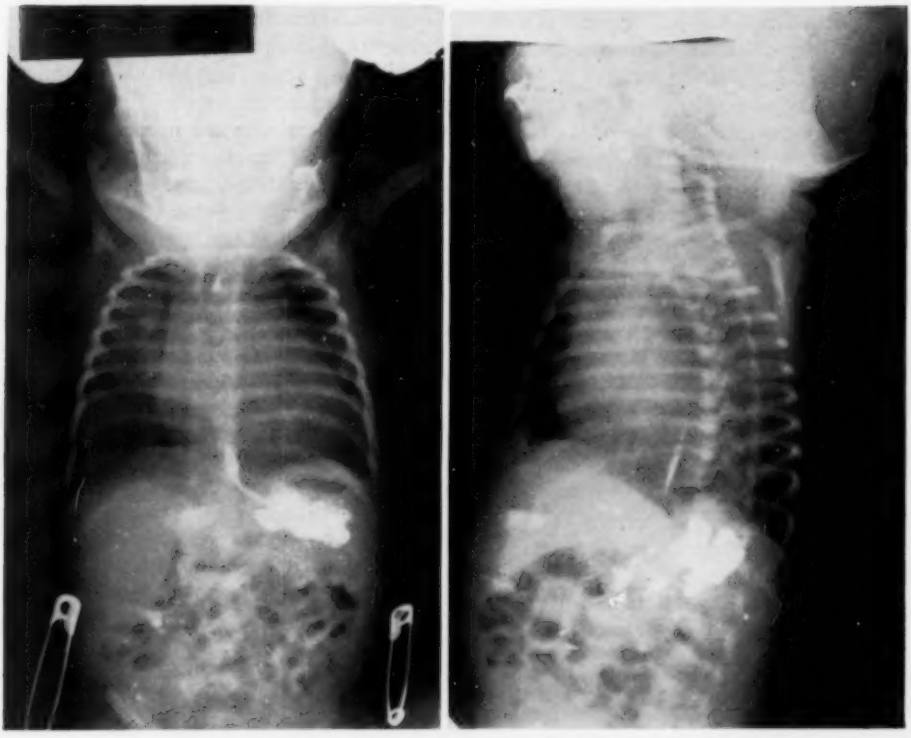

Fig. 2.—Roentgenograms of the chest, posterior-anterior and left anterior oblique positions, showing left ventricular enlargement.

measured approximately 0.5 cm. in its greatest diameter. The right ventricle and the tricuspid and pulmonary valves were normal. The left auricle was dilated, and the endocardium was markedly thickened and yellowish white. The mitral valve was slightly thickened, but the chordae were not shortened to any extent. The left ventricular endocardium was also yellowish white, but this process was not so marked as in the left auricular endocardium. The aortic valve was markedly stenosed by thickened adhesive edematous-appearing cusps giving an appearance similar to vegetations of verrucose endocarditis. This was interpreted, however, as part of the process of endocardial sclerosis, which was evident in the rest of the structures of the left side of the heart.

On microscopic section, the left ventricular myocardium was thickened. The muscle bundles were hypertrophied, and there was pleomorphism of the nuclei. The epicardium was notable only for the congestion of the blood vessels. In the endocardium there was a moderate thickening of the subendocardial portion, particularly in the columnae carneae and in the Thebesian system. Section through the auricular endocardium and myocardium revealed marked thickening of the endocardium by fibroelastic tissue and some hypertrophy of the musculature. A section through the aortic valve revealed a fibromyxomatous thickening, which at the base appeared to be almost cartilaginous. There was a basophilic smudging in the center of the leaflets. The aorta was not remarkable. The left ventricular musculature was hypertrophied, but the endocardium, except immediately adjacent to the valve, was not thickened to any appreciable extent.

COMMENT

Valvular involvement as part of the process of endocardial sclerosis is not an uncommon finding.* Dennis [8] in a recent review of the literature found that the valves were affected in 51% of the cases. Despite this high incidence, extreme stenosis of the aortic valve in association with endocardial sclerosis is rarely encountered.

* References 2-7.

A discussion of the pathogenesis of endocardial sclerosis in association with aortic stenosis is not within the scope of this paper. An excellent bibliography on this subject is available in the review by Torp.[9] In the case reported here, the fact that the left atrium was more severely affected than the left ventricle indicates that the endocardial sclerosis did not occur as a result of the aortic stenosis. It would appear then that the aortic stenosis in this patient was either a separate and primary condition or was a part of the process of endocardial sclerosis. Whatever the basis, it is to be recognized that these two conditions do occasionally coexist, and, when such is the case, accurate diagnosis during life may be difficult or even impossible.

The diagnosis of congenital stenosis at or below the aortic valve is generally not a difficult one. The loud harsh systolic murmur and thrill, maximal at the base of the heart to the right of the sternum and transmitted up the neck vessels, are characteristically present. Because of the resistance to the outflow of systemic blood, the peripheral pulses are often weak. Enlargement of the left ventricle may be demonstrable by electrocardiogram and teleoroentgenogram, and clinically there may be evidence of left ventricular failure. Other conditions causing enlargement of the left ventricle must be differentiated. These include endocardial sclerosis alone, patent ductus arteriosus, coarctation of the aorta, anomalous origin of the left coronary artery, and congenital mitral insufficiency. When endocardial sclerosis occurs in addition to the aortic stenosis, the findings characteristic of the latter may be exaggerated but not appreciably altered. This unusual combination should probably be suspected in all cases of aortic stenosis in which cardiac failure occurs early in infancy.

In the case presented there was little doubt that the patient was suffering from either an aortic or a subaortic stenosis. Moreover, the episodes of failure suggested that either the stenosis was of extreme degree or there were associated anomalies. It was my belief that this child would not survive without surgical intervention. Surgical relief of the aortic stenosis when associated with endocardial sclerosis is obviously extremely hazardous. Had the patient survived the operation, the altered endocardium would have continued to interfere with the normal excursion of the involved chambers. In the light of our present knowledge, however, attempts at surgical relief of the aortic stenosis appear justified, especially since recent evidence suggests that endocardial sclerosis is not uniformly fatal during childhood.[10]

SUMMARY

The clinical and pathological features of the case of a 5-week-old infant with congenital aortic stenosis probably due to endocardial sclerosis are reported. An aortic valvulotomy was performed, but the patient did not survive the operation. The diagnosis and treatment of cases of this type are discussed. Aortic valvulotomy, although extremely hazardous, is probably justified.

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CONGENITAL STENOSIS OF PROSTATIC URETHRA

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OBSTRUCTION of the posterior urethra in infants, contributing to or resulting in death, is not rare. Bugbee and Wollstein,[1] in 1924, reported 38 cases of hydronephrosis resulting from posterior urethral obstruction, in a series of 4903 autopsies at Babies Hospital, New York City. Posterior urethral valve formation was the commonest cause, and hypertrophy of the verumontanum, the second. There were no cases of congenital stenosis of the posterior urethra in this series.

Congenital stenosis of the posterior urethra is one of the rarest of all urinary tract anomalies.* Dourmashkin,[2] in 1943, reviewed the literature and reported only one case of complete occlusion of the prostatic urethra in a living newborn infant.

The following fatal case of congenital stricture of prostatic urethra in a newborn infant is reported because of paucity of such cases in the literature and because the awareness of a surgically correctable congenital posterior urethral obstruction on the part of the obstetrician or pediatrician can be life-saving.

REPORT OF CASE

The mother was a healthy 33-year-old multipara. A 3200 gm. white boy was delivered without difficulty after a four-hour period of labor as a breech presentation. The baby had a markedly distended abdomen at birth, was livid rather than cyanotic, and had weak respirations and retraction of right side of chest. The obstetrician, preoccupied by the weak respirations rather than the distended abdomen, aspirated the baby and put him in an oxygen airlock. The child died four hours after birth.

Submitted for publication Jan. 6, 1956.

From Division of Laboratories, St. Mary's Hospital.

* References 1-3.

At necropsy, 11 hours after death, the bulging abdomen was found to be due to an enormously distended and obstructed urinary bladder (Fig. 1). The bladder was twice the size of the liver. Bilateral hydroureters and cystic kidneys were noted. Despite tremendous pressure on the bladder by the prosector, urine could not be expressed through the urethra. A fine probe could be easily passed through the anterior two-thirds of the urethra. An obstruction, which could be passed with difficulty, was met in the posterior one-third of the urethra. The anterior wall of the hypertrophied and dilated bladder was opened, and the posterior urethra was probed. It was impossible to pass the probe through the prostatic urethra (Fig. 2). The verumontanum, readily seen in the normal urethra of a 7-month boy (Fig. 3), was not visible in this case because of pressure atrophy (Fig. 2). The proximal part of the prostatic urethra was dilated (Fig. 2). The distal prostatic urethra was stenosed by an annular constriction with a diameter less than 0.5 mm.

Fig. 1.—Genitourinary tract, unopened, showing obstructed, distended bladder, bilateral hydroureter, hydropelves, and enlarged cystic kidneys. Compare size of normal opened aorta with kidneys and bladder.

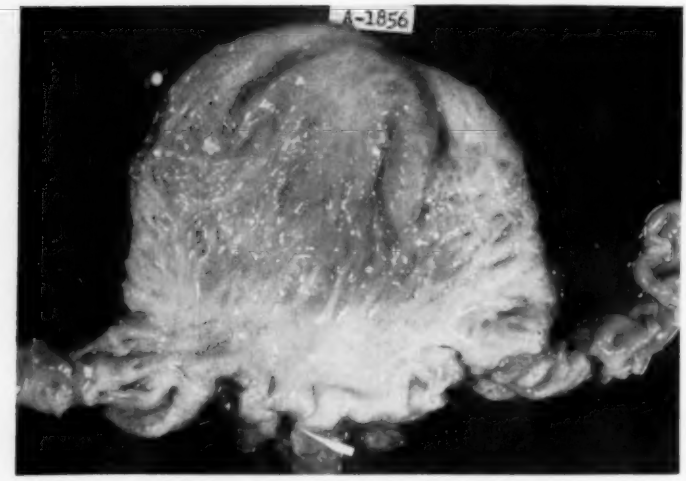

Fig. 2.—Bladder and prostatic urethra. Arrow points to area of stenosis. The proximal portion of the prostatic urethra is dilated. The verumontanum is not visible because of pressure atrophy. Bladder is dilated, trabeculated, and hypertrophied.

Posterior urethral valves were carefully searched for but were not found (Fig. 2). The mucosa of the bladder was trabeculated, and the wall was thickened up to 2.5 cm. The unopened ureters, which were kinked due to adhesions and elongated, had a diameter greater than the sigmoid colon (Fig. 1). The pelves and calyces of the kidneys were dilated and thickened, replacing a large part of the medullae and cortices (Fig. 3). The urethral obstruction had resulted in bilateral hydroureters and hydronephrosis (Fig. 3).

Microscopic Findings.—The mucosa of the prostatic urethra at the point of stricture consisted of stratified squamous epithelium instead of the usual transitional-cell epithelium. The stroma between the mucosa and the muscularis showed marked fibrous thickening. The lumen of the urethra was markedly narrowed. There was thickening of the bladder wall and hydronephrosis of the kidneys.

The heart, brain, liver, spleen, and other parenchymatous organs were unremarkable. The lungs showed a moderate degree of atelectasis and congestion.

COMMENT

The urethra, embryologically, consists of three different portions, each developing separately and then uniting with each other. The prostatomembranous portion, endodermic in origin and derived from the urogenital sinus; the cavernous portion, de-

Fig. 3.—Genitourinary tract of newborn infant, opened, showing stenosis of prostatic urethra, dilated and hypertrophied bladder, bilateral hydroureter, and hydronephrosis. Note adjacent specimen of urethra with verumontanum, bladder, and ureter of normal seven-month infant.

rived from the genital gutter, ectodermic in origin, and the portion of the urethra consisting of the meatus and fossa navicularis, developing later from a distinct epithelial layer, are three different embryological structures which go into the formation of the urethra. The location of the urethral occlusions often corresponds exactly with the points of their union. In the majority of the living newborn infants studied and reviewed by Dourmashkin,[3] the occlusion involved the penile urethra.

In the two best-described cases of posterior urethra obstruction, one was in a newborn infant who did not void because of an obstruction in the prostatic urethra.[2] A whalebone filaform bougie was successfully passed through the obstruction. The second case, described by Crowell and Anderson,[4] was in a 7-week-old boy who had acute urinary retention due to an annular stricture of the prostatic urethra. This child died of uremia, with a hypertrophied bladder and bilateral hydroureters and hydronephrosis.

Campbell,[5] in discussing congenital urethral strictures, states that they are characterized simply by abnormal narrowing of the canal without localized periurethritis and by dilatations of the urethra proximal to the stricture. These were exactly the findings in this case.

Urinary excretion begins about the fifth month of fetal life.[6] In this case, the posterior urethral obstruction was present a long time before birth, as evidenced by the tremendous dilatation and hypertrophy of the bladder and extensive bilateral hydronephrosis found at age one day.

It is likely that this baby would not have survived despite relief of urinary bladder obstruction by cystostomy. Nevertheless, other children may be saved if the rare condition of posterior urethral obstruction is thought of as the cause of abdominal distention in the newborn.

SUMMARY

A fatal case of annular stricture of prostatic urethra of a one-day-old baby is presented.

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AN ACUTE MASSIVE OVERDOSE OF POLYMYXIN B SULFATE

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and
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WE WISH to report a case of intoxication from a single massive dose of polymyxin B sulfate with apparently a satisfactory response to tripelennamine (Pyribenzamine). Polymyxin B sulfate is a bactericidal antibiotic derived from Bacillus polymyxa and composed of polypeptides and a fatty acid. Its use has been limited because of three types of toxic effects: neural, cutaneous, and renal.[1] Neurotoxic side-reactions include paresthesias, dizziness, ataxia, and dysarthria. Renal toxicity seldom appears unless the dose is over 2.5 mg. per kilogram per day.[2] Then albuminuria is common, and oliguria and nitrogen retention have been reported. Cutaneous reactions (urticarial and maculopapular rashes) respond to antihistamines.[3] Neurotoxic effects disappear within 24 to 48 hours, and signs of renal toxicity usually are gone four days after the drug is discontinued.

Although the toxic effect of a large overdose of polymyxin in animals has been studied,[5] there are no reports as to the effect of an acute overdose of polymyxin in humans. It is our purpose to present observations on an infant receiving a single massive overdose and the response of the toxic symptoms to tripelennamine.

REPORT OF CASE

A 5½-month-old white boy weighing 3000 gm. had been treated two months for congenital posterior urethral obstruction, with bilateral pyelonephritis, hydronephrosis, and hydroureter. Repair of the urethra had been effected, and drainage was instituted through suprapubic and urethral catheters. In spite of drainage and antibiotic therapy, infection persisted, and finally two organisms predominated, Pseudomonas aeruginosa and Proteus morganii, which were both sensitive only to polymyxin.

High fever and marked anorexia forced the decision to use polymyxin B (Aerosporin) in spite of existing renal damage with albuminuria and an elevated blood nonprotein nitrogen level. Four equal doses, totaling 2.5 mg. per kilogram per day intramuscularly, were ordered. Accidentally the third dose administered was 50 mg., or 16.6 mg. per kilogram. One and one-half hours later the infant was found to be in acute distress. Examination revealed a severe generalized erythema, his appearance fully deserving the description "boiled lobster." He was irritable, agitated, and obviously quite uncomfortable, attempting scratching movements. Respirations were 30 per minute and gasping. There was a slight circumoral cyanosis. The chest was clear, and the pulse rate was 130 per minute. Peristalsis was hyperactive, and vomiting occurred several times. He quieted somewhat after secobarbital (Seconal) sedation and oxygen. Nine hours after the toxic dose of polymyxin he showed only slight improvement, and 2 mg. of tripelennamine was given intramuscularly. Within an hour the skin color and respirations were normal and the agitation had vanished. Tripelennamine, 4 mg. every four hours, intramuscularly, was continued for two days.

Renal damage was expected and fluid intake reduced in anticipation of oliguria. Accurate records of urine volume were not possible because of urine leakage around the cystostomy catheter. After three days on a reduced fluid intake he became clinically dehydrated. The blood nonprotein nitrogen level was elevated, and urine volume seemed diminished. Fluid intake was increased, and diuresis occurred on the fifth and sixth days after the toxic dose of polymyxin. Thereafter the urine output was at pretreatment levels. The urine was sterile on culture 24 hours after the massive dose of polymyxin, and pyuria disappeared, although albuminuria persisted. Improvement in the patient's general status was evident. In the following weeks pyuria and systemic signs of infection returned, and another course of polymyxin was given in the usual dosage without toxic effect.

Submitted for publication Nov. 17, 1955.

From The Children's Hospital and Department of Pediatrics, University of Cincinnati College of Medicine.

COMMENT

The amount of polymyxin received by this infant was within the fatal range for a single injection in laboratory animals.[5] He survived the first critical hours with oxygen and sedation, but his condition improved greatly after the injection of tripelennamine. Recovery was complete in 10 hours, rather than the expected 24 to 48 hours. Tripelennamine had been used previously in controlling the skin and gastrointestinal manifestations of polymyxin therapy with good results.

In animals there is evidence that polymyxin causes release of histamine.[6] The picture presented by this patient resembled acute histamine poisoning, with peripheral flush, hyperperistalsis, vomiting, and possible paresthesias.[7] The prompt and gratifying response to tripelennamine supports this concept as to the nature of the toxic effect.

SUMMARY

The history of an infant receiving a single large and potentially fatal dose of polymyxin is presented. Toxic signs occurred which resembled the response to a large dose of histamine. Tripelennamine appeared to be specific in alleviating the symptoms.

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THE MALE TURNER SYNDROME

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TURNER,[1] in 1938, presented a syndrome of infantilism, congenital webbed neck, and cubitus valgus in seven short girls ages 15 to 23 years. Since then, many similar cases have appeared in the literature,* and the syndrome has been further elaborated. The essential features were categorized in 1953 by Jackson [5] under three headings:

(1) gonadal agenesis, with resultant primary amenorrhea, poorly developed secondary sex characteristics, increased gonadotropin, and diminished 17-ketosteroid excretion

(2) skeletal defects, including short (not dwarfed) stature, a constant finding, and a group of anomalies commonly, though not invariably, found, as webbed neck, short neck, cubitus valgus, shield-shaped chest, wide arm span, fused cervical vertebrae, and shortened phalanges

(3) associated nonskeletal anomalies, including mental retardation, ocular and renal defects, and vascular anomalies, such as coarctation of the aorta and hypertension without coarctation.

The first case of the Turner syndrome in the male was reported by Flavell,[6] in 1943, and has been followed by at least the 10 cases listed in the Table.† These cases fulfilled the diagnostic criteria of this syndrome. Either one or both testes were present and were underdeveloped in every case except one.[14] Short stature was common to all, while webbed neck and cubitus valgus were the commonest associated skeletal defects. The values for 17-ketosteroid excretion were low to low normal, and those for urinary gonadotropins varied from low to high.

The male patient herein described also possesses the essential characteristics of the Turner syndrome and in addition has two associated skeletal anomalies never previously reported.

REPORT OF CASE

A white boy was first seen at 11 years of age for short stature, cryptorchidism, and poor speech.

His birth was at term following an uneventful pregnancy; his weight was 7 lb. 14 oz. and he was of average height. He was born with the cord around his neck, was given oxygen therapy, and had many convulsions in the first week of life. His neonatal development was retarded, as observed in his difficulty in sucking, slow increase in weight and height, holding his head up at 9 months, late eruption of teeth, sitting at 18 months, walking at 2 years, and talking poorly at 4 years. Although his speech improved with special training for many years, it still was abnormal at 11.

Bilateral cryptorchidism was the only abnormality noted at birth. At 18 months of age this was treated with 12 "injections" of unknown type, and again at 6 years there were 16 injections of unknown amounts of chorionic gonadotropin. Six months later the left testis descended into the scrotum.

The family history showed neither retardation in somatic or genital development nor anomalies of the skeleton or other organs. The father and 17-year-old brother were 5 ft. 8 in. and 5 ft. 10 in. tall, respectively. The mother's height was 5 ft. 1 in.

The boy's height was 51½ in. His lower longitudinal measurement was 26½ in.; span was 54 in., and he weighed 82 lb. Although he was alert and responded well to questions, his nasal voice and poor speech made comprehension difficult. The somatic findings were normal except for the short neck, cubitus valgus, and shield-shaped chest. The genitals, including the phallus, scrotum, and left testis were properly formed. The estimated volume of the latter was 1½ cc.[16] The right testis was not palpable within the scrotal sac or inguinal canal. No pubic or axillary hair was present.

For the next five years, ages 11 to 16, the patient received many therapies to accelerate somatic and

Received for publication Nov. 30, 1955.

This work was supported with funds from the Jewish Philanthropic League of Brooklyn.

* References 2-4.

† References 6-15.

Features of the Male Turner Syndrome

	Testes	Sperm	Penis	Potency	Body Hair	Voice	Gyneco-mastia	Stature	Span	Congenital Anomalies	Osteo-porosis	17-Keto-steroids, Mg.	FSH, M. U.*	Testis Biopsy
Flavell [6] (1943)	Small	.....	Normal	Normal	Sparse & female	High	No	Short	.....	Webbed neck, cubitus valgus, cervical spina bifida	.....	.....	.....	.....
McCullagh [7] (1948)	Small	.....	.....	.....	.....	High	.....	Short	.....	Webbed neck, cubitus valgus, microph-thalmos	.....	Low	Normal	Hypoplasia; no Leydig cells
Greenblatt [8] (1948)	Small	Azoo-spermia	Large	.....	.....	.....	.....	Short	.....	Webbed neck, cubitus valgus	.....	Low normal	Normal	Tubular hypoplasia; Leydig cells present
Reforzo-Membrives [9] (1949) (12 yr.)	Small	.....	Normal	.....	.....	.....	.....	Short	.....	Webbed neck, cubitus valgus, epicanthic folds	Yes	Low	Low	As in pituitary dwarf-ism; Sertoli cells present
Sohval [10] (1951)	Small	No semen	Small	No ejaculation	Sparse & female	Mascu-line	Yes	Short	.....	Cubitus valgus, cervi-cal vertebral anomalies	No	Low normal	High	Tubular aplasia; Ley-dig cells present
Sougin-Mibashan [11] (1953)	Small	No semen	Normal	Totally impotent	Very hairy	Highish	No	Short	Wide	Webbed neck, no valgus	Yes	Low	High	.....
Oster [12] (1954) (12 yr.)	Small; at exter-nal ring	.....	Small	.....	.....	.....	.....	Short	.....	Cubitus valgus, short 5th finger, prehensile toes, genu valga M. R.	.....	1.5	50	.....
Cunningham [13] (1951) (7 yr.)	Unde-scended	.....	Small	.....	.....	.....	.....	.....	.....	Webbed neck, mod. cubitus valgus	.....	1.1	6	A. P. L.† resulted in de-scent of testes & enlarge-ment of penis
Dorf [14] (1948)	Under-developed	.....	Under-developed	.....	.....	.....	.....	Short	.....	Webbed neck, enlarged head	.....	0.55	Neg. for 80	.....
James [15] (1952) (2 3/12 yr.)	Normal size; at external ring	.....	Small; 2.5×1 cm.	.....	.....	.....	.....	32 in. at 27 mo.	.....	M. R. pterygium, hypo-tonia, abnormality of toes, potential cubitus valgus	Yes, in long bones	1.6	8	.....
Present case (11 yr.)	Left, 1.5 cc.; right, un-descended	.....	Prepu-bertal	.....	Few pubic strands; no axillary	High; nasal	None	Short; 57½ in.; 3% line	Wide	Short neck, shield chest, cubitus valgus, speech defect	No	1.2	41	.....

* Follicle-stimulating hormone, mouse units.
† Chorionic gonadotropin, Ayerst.

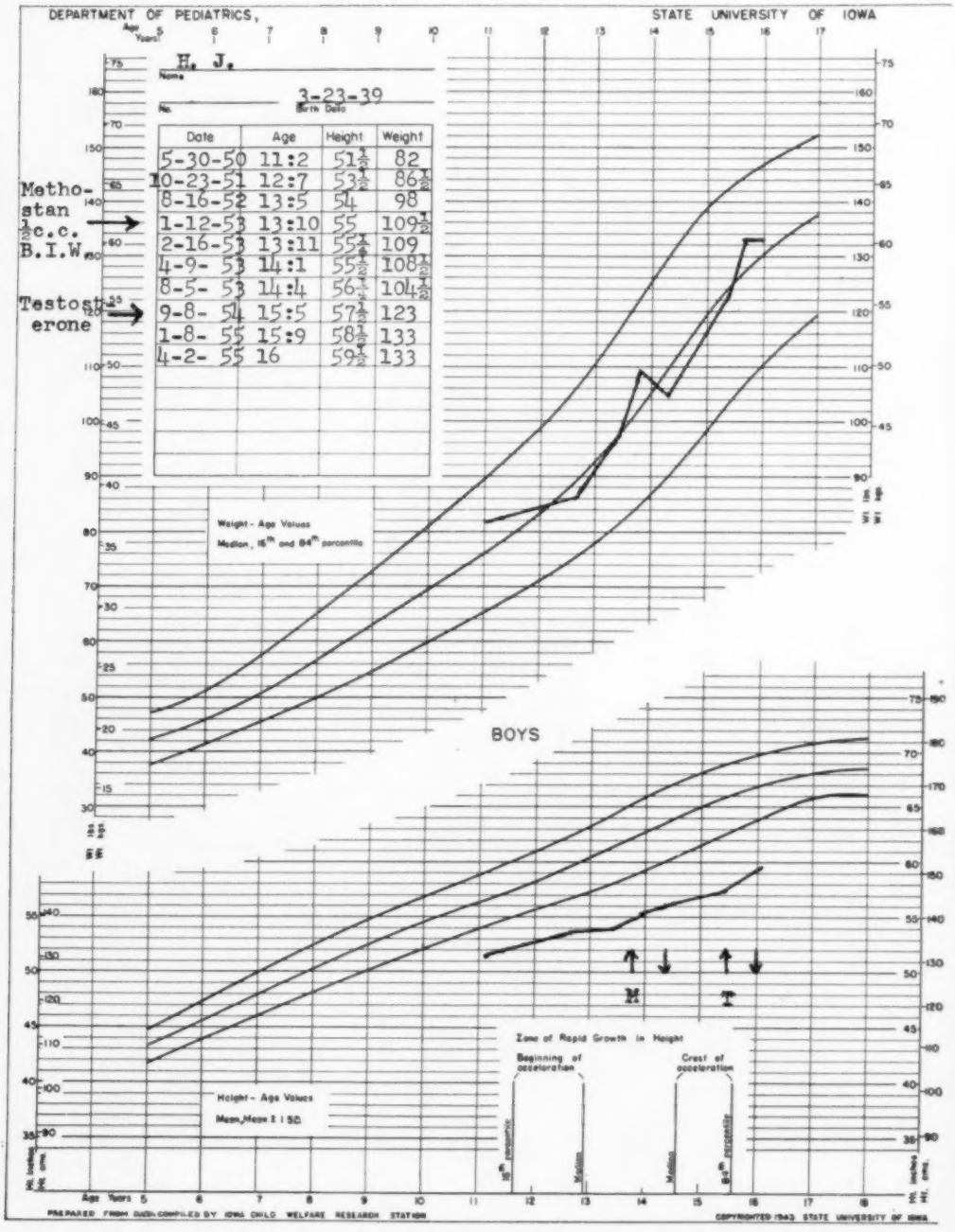
DEPARTMENT OF PEDIATRICS,
STATE UNIVERSITY OF IOWA
Name H. J.
No.
Birth Date 3-23-39
Date | Age | Height | Weight
5-30-50 | 11:2 | 51½ | 82
10-23-51 | 12:7 | 53½ | 86½
8-16-52 | 13:5 | 54 | 98
1-12-53 | 13:10 | 55 | 109½
2-16-53 | 13:11 | 55½ | 109
4-9-53 | 14:1 | 55½ | 108½
8-5-53 | 14:4 | 56½ | 104½
9-8-54 | 15:5 | 57½ | 123
1-8-55 | 15:9 | 58½ | 133
4-2-55 | 16 | 59½ | 133
Metho-stan ½ c.c. B.I.W.
Testosterone
Weight - Age Values
Median, 16th and 84th percentile
BOYS
Zone of Rapid Growth in Height
Beginning of acceleration
Crest of acceleration
Height - Age Values
Mean, Mean ± 1.50
Age Years
PREPARED FROM DATA COMPILED BY IOWA CHILD WELFARE RESEARCH STATION
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Fig. 1.—Height and weight curves for five-year period.

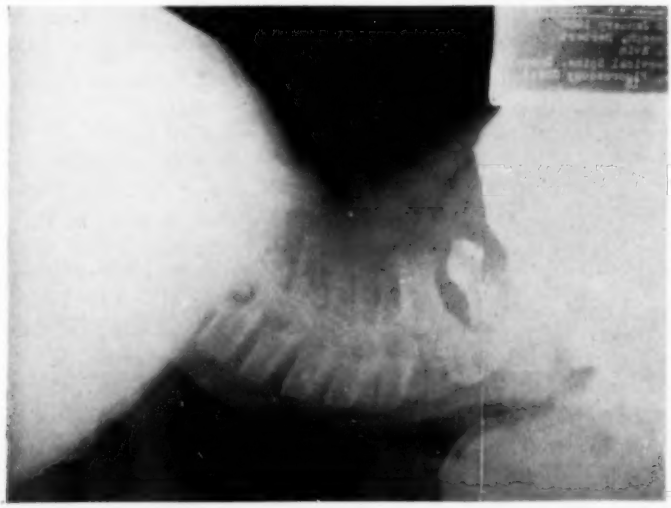

Fig. 2.—Short vertical diameter C-3-4-5-6.

genital growth (Fig. 1). After a 10-month course of 750 units twice weekly of chorionic gonadotropin (A. P. L.‡) his height was only 54 in. and his genitals were unchanged. A seven-month trial of 25 mg. twice weekly of methylandrostenediol § was similarly unrewarding, except for increased size of the phallus and the appearance of pubic hair. The final medication of 800 mg. Depo-testosterone ‖ over a six-month period resulted in a height increment of 2 in., a 10 lb. weight gain, and a further increase in phallic size and pubic hair.

‡ A. P. L., Ayerst Laboratories, Inc.

§ Methostan, Schering Corporation.

‖ The Upjohn Company.

The hemogram, urine analysis, serum glucose, cholesterol, calcium, phosphorus, and alkaline phosphatase were within physiologic limits. The 24-hour urine excretion of 17-ketosteroids was 1.2 mg. and remained essentially unchanged during the period of therapy. The gonadotropin excretion value was 41 mouse uterine units (m. u. u.) during a period when no hormone was being administered. Biopsy of the testis was refused.

Roentgenographic studies of the skull were not remarkable, but those of the cervical spine and hand revealed interesting anomalies (Figs. 2 and 3). On

Fig. 3.—Long proximal phalanges and unusual contouring of metacarpals.

the lateral view, the bodies of the third, fourth, fifth, and sixth cervical vertebrae, when compared with the norm, were flatter, with shorter vertical diameters. The proximal phalanges of the hand were unusually long, and the tubulation of the metacarpals was unusual in that the distal halves of the shafts were somewhat squarer and showed less contouring than average. No osteoporosis was seen. The bone age as determined by the epiphyseal development of the hand [17] was 10½ years at age 11, and after hormone therapy bone age was only 14 years at age 15¾.

COMMENT

In the classical female Turner syndrome no recognizable ovarian tissue is found and secondary sex characteristics are ill-defined or absent. However, a feminine genital tract is always present. This is in accord with the experimental work on rabbit [18] and mouse [19] embryos, where destruction of the gonads prior to sexual differentiation produces fetuses with feminine genital tracts irrespective of the genetic sex of the embryo. Clinical support and application of this work is aided by the study of chromosomal patterns in skin biopsies. Polani, Hunter, and Lenox [20] described three "female" cases of Turner's syndrome with male chromosomal patterns and feminine genital organs. It is suggested that these cases are examples of genetic males with interruption of gonad maturation prior to testicular differentiation.

Genetic males without gonads and with female genital tracts on the one hand and genetic males with testes and male genitalia on the other may lend weight to the theory [21] that the gonads are zygotically determined, while genital tract differentiation is hormonally influenced. This would possibly explain why a search of the literature fails to reveal a single report of the counterpart of the Turner syndrome in the male in which there is complete absence of testicular tissue. Furthermore, it is quite probable that the patient herein described, as well as those previously referred to in Table 1, is an example of the male Turner syndrome in which gonadal arrest took place later in embryonic development, when recognizable hypofunctioning testes were formed. The findings are similar to Wilkins and Fleischmann's [4] histologic observations in ovarian developmental arrest.

In primary hypogonadism one usually finds an elevated value for urinary gonadotropins. The quantity (41 m. u. u.) in this 15-year-old boy is not increased. No clarification is at hand, since testis biopsy was refused. An explanation was offered by Reforzo-Membrives [9] in a similar situation in a 12-year-old boy whose testis had Sertoli cells with poorly defined germinal epithelium and no Leydig cells. These authors believe with Del Castillo [22] that the Sertoli cells produce a substance comparable to estrogen, which can regulate the secretion of follicle-stimulating hormone by the pituitary. This explanation may be germane to our case.

On clinical grounds, however, the primary nature of the gonadal deficiency in this patient gains support from the fact that administration of chorionic gonadotropins for a long period of time in fairly large dosage failed to cause phallic enlargement or to initiate sexual hair growth. This would have occurred if the hypogonadism were secondary to pituitary insufficiency. Furthermore, it is significant that substitution therapy (methylandrostenediol and testosterone) did result in increased size of the penis, pubic hair growth, deepening of the voice, and heavier musculature.

The patient's weight and height for a five-year period are charted in Figure 1. The first two years represent a control period prior to the courses of chorionic gonadotropin, methylandrostenediol, and testosterone. It will be noted that no appreciable alteration in the rate of growth occurred at any time; nor was there acceleration of bone maturation during the periods of therapy. Since an increase in both growth rate and skeletal maturation results as a rule from the administration of testosterone in both the normal prepuberal boy and the hypogonadal patient, the lack of response in this patient may support the belief that his slow rate of growth is in no way related to his gonadal insufficiency but is a genetic defect.

In addition to the short stature and hypogonadism, the patient presented cubitus valgus, wide span, and shield-shaped chest. The short neck results from the flattened bodies of the third, fourth, fifth, and sixth cervical vertebrae. The increased length of the phalanges of the hand and the changes in contouring and tubulation of the metacarpals represent additions to the long list of skeletal defects already described in this syndrome.

SUMMARY

A case of the male Turner syndrome in an 11-year-old boy is presented.

The characteristic short stature, cubitus valgus, and hypogonadal state are described.

Anomalies of the cervical vertebrae, metacarpals, and phalanges of a type not previously reported are noted.

The significance of the failure of therapy to alter the growth curve is pointed out.

The implications of zygotic versus hormonal influences in genital tract differentiation are briefly discussed.

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CONGENITAL TRACHEOESOPHAGEAL FISTULA WITHOUT ATRESIA OF THE ESOPHAGUS

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INTRODUCTION

SURGICAL correction of tracheoesophageal fistula without atresia of the esophagus has been reported 15 times in the American medical literature.* This additional case is being reported to review symptoms of the lesion and to clarify methods for confirming the diagnosis. Tracheoesophageal fistula was diagnosed at age 3 months by a modification of the radiological technique described by Cardullo and Berens.[3] The fistula was closed at thoracotomy, but the patient died on the second postoperative day from malnutrition and bronchopneumonia.

REPORT OF CASE

This 2-day-old white boy was the product of an uncomplicated delivery, weighing 5 lb. 8 oz. Physical examination revealed a hypoplastic right thumb and excessive pharyngeal mucus. The baby choked, regurgitated, and became cyanotic with feedings, and was referred to Childrens Hospital with a diagnosis of tracheoesophageal fistula with esophageal atresia. On arrival, a gastric tube was easily inserted into the stomch and gastric juice withdrawn; the tube was left in place for feeding. On the fourth day, iodized oil U. S. P. (Lipiodol) swallow showed a patulous cardiac orifice of the stomach which allowed regurgitation with aspiration of contrast media into the bronchi. The continuity of the esophagus was intact, without demonstrable fistula. Skeletal x-rays revealed an absent right first metacarpal and thumb, synostosis of the right first and second ribs, two hemivertebrae at the level of the ninth thoracic vertebral body, and incomplete segmentation of the fifth sacral and the first coccygeal vertebrae. The infant improved on thickened feedings and was discharged with diagnoses of chalasia and multiple skeletal anomalies.

The patient was readmitted at age 2 months with explosive diarrhea and at 2½ months with an ear infection. He had had occasional episodes of choking and cyanosis associated with feedings during the interim. Thickened feedings had been continued, and he weighed 2 lb. more than birth weight. During his third hospital stay the infant had an episode of respiratory distress associated with marked abdominal distention which responded to oxygen and gastric suction. He was rehospitalized with bronchopneumonia at age 3 months. Now the physical examination revealed an emaciated, chronically ill 7 lb. youngster with rales throughout his chest. Chest x-ray showed severe bilateral aspiration pneumonitis. Radiography with iodized oil and fluoroscopy of the esophagus failed to show tracheoesophageal fistula. Because of continued aspiration, the esophagus was examined by the technique described herein, and escape of iodized oil from the midesophagus into the trachea was shown. An anomalous right subclavian artery was also demonstrated. Esophagoscopy failed to confirm the presence of the fistula. At thoracotomy the tracheal opening of the fistula was found 1 cm. above its esophageal orifice. The tract was divided and sutured. Two days postoperatively the infant died from sudden circulatory collapse. Autopsy findings revealed circulatory and respiratory pathology. The aorta occupied its usual position, but the vessels originating from the arch showed abnormalities.

Proximally the largest of three ostia of the aortic arch opened into two large branches which formed the right and left common carotid arteries. The second ostium originated the left subclavian artery. The third opened into a vessel coursing to the left of the mediastinum and crossing to the right behind the esophagus and trachea. This vessel gave origin

Submitted for publication Dec. 19, 1955.

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*References 1 and 2.

to the right vertebral artery and continued as the right subclavian artery. Bronchopneumonia was present and confirmed microscopically. The mid-third of the esophagus revealed a V-shaped structure, with the apex of the "V" directed superiorly and a small patent orifice below the apex. This opening easily admitted a probe into a 1 cm. fistulous tract between the esophagus and trachea. The surgical repair was intact, and the remainder of the esophagus was normal. A Meckel diverticulum was found on examination of the small bowel.

COMMENT

Tracheoesophageal fistula with atresia occurs about once in every 5000 live births in the Boston area.[4] Up to 1946, nearly 100 patients with tracheoesophageal fistula with esophageal atresia had been seen at the Boston Childrens Hospital, but none with the fistula alone.[5] In 1945, Leven and Lannin [6] reported 41 cases of tracheosophageal fistula, 2 of which were unassociated with esophageal atresia. Neither was corrected surgically. In 1946, Holt and co-workers [7] reported 46 cases with atresia and 1 without atresia. The first case cured by surgery was reported in 1939.[8] The child had a stricture of the esophagus, and, in dilating it, the dilating string passed into the trachea. Dr. Chevalier Jackson performed bronchoscopy and saw the fistula, which was later closed through a tracheotomy incision. In 1948, Haight [9] closed a tracheoesophageal fistula in a 4-year-old boy by a thoracotomy procedure. Ferguson,[5] in 1951, reported three other cases in which the fistula was surgically closed. The roentgen studies were done in these cases by having the patient swallow iodized oil.

Herweg and Ogura [2] reported three cases without associated esophageal atresia, two of which were surgically repaired. The preoperative diagnosis was confirmed by a technique utilizing methylene blue, endotracheal tube, and esophagoscopy. Eight other isolated cases of this lesion corrected surgically have been reported.[2] Over 100 cases of tracheoesophageal fistula have been admitted to the Los Angeles Childrens Hospital, and the present case is the only example without associated esophageal atresia. The cardinal symptoms are regurgitation, cyanosis, and coughing associated with feeding. Excessive pharyngeal mucus usually is not present, although it was observed early in our case. Abdominal distention may or may not be a prominent feature. Chronic cough, inanition, and bronchopneumonia follow. Since the fistula is epithelialized, closure does not occur spontaneously, and progressive pulmonary damage and malnutrition occur. The diagnosis was not established early in our case because routine radiographic examinations of the esophagus had failed to show the lesion. Such patients are poor surgical risks because of chronic malnutrition and constant aspiration resulting in recurrent lower respiratory infection. Once the diagnosis is established, repair should be accomplished without delay.

An anomalous right subclavian artery was observed in the present case and was described in 3 of the 15 cases reviewed. The fistula is located above the constriction of the esophagus by the anomalous vessel, and ingested material tends to be forced through the fistula into the trachea. Although this may augment the patient's symptoms, it also facilitates visualization of the fistulous tract by radiographic methods.

ROENTGEN FINDINGS AND TECHNIQUE

From the esophageal opening, the fistulous tract gradually decreases in caliber and curves upward to enter the trachea at a higher level. It resembles the spout of a miniature teapot. This appearance is seen in our case and in all the pictures found in the literature. The "tenting" of the esophagus is seen when only the base of the fistula is filled. In the embryo, the esophagus increases in length more than the trachea, so that the fistula is stretched into a slanting upward curve.

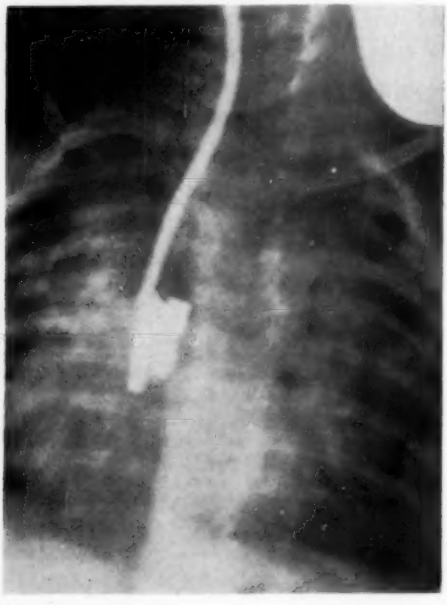
In our case the technique of Cardullo and Berens [3] was modified by using iodized oil rather than iodopyracet (Diodrast). The patient must be prone during injection so that gravity will aid passage of the contrast substance into the fistula. If contrast sub-

stance is taken by mouth, aspiration may occur and presence of media in the trachea will not be evidence of a fistula. If it is injected into the esophagus and does not reflux into the pharynx, it can only reach the trachea through a fistula. In our case the presence of iodized oil in the bronchi following this study proved the presence of a fistula.

The tip of a rubber catheter is placed in the midportion of the esophagus and securely held in place by adhesive tape. Two to three cubic centimeters of iodized oil are then rapidly injected into the esophagus. Both fluoroscopy and spot films are needed to follow the course of the injected material. If the esophagus is normal, the iodized oil will pass rapidly into the stomach. If there is a fistula, some oil will usually pass into the trachea. Every effort should be made to prevent regurgitation into the pharynx.

Figure 1 demonstrates the position of the catheter in the esophagus with the tip of the tube near the level of the carina. Iodized oil

Fig. 1.—Demonstration of the position of the catheter in the esophagus, with the tip of the tube near the level of the carina.



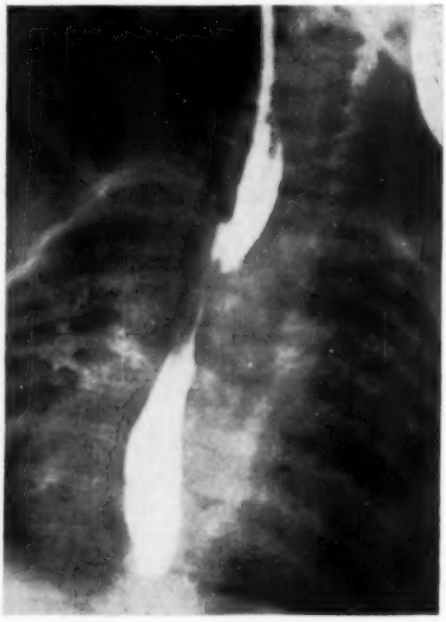


Fig. 2.—This Figure shows the "tenting" of the anterior wall of the esophagus at the site of the fistula.

was injected at that point and later was shown in the main-stem bronchi without reflux into the pharynx. The next spot film shows the "tenting" of the anterior wall of the esophagus at the site of the fistula (Fig. 2.). A later film shows the characteristic defect in the posterior wall of the esophagus due to the presence of an anomalous right subclavian artery (Fig. 3). The final film demonstrates the filling defect of an aberrant right subclavian artery, and slightly above, the iodized oil outlines the tract of the fistula curving upward to enter the trachea (Fig. 4) and is seen spreading over the posterior wall of the trachea. The value of this special technique of roentgen examination cannot be overemphasized. Repeated examinations of this patient by routine methods failed to demonstrate fistula for two reasons:

1. It was thought that the contrast substance in the trachea had been aspirated from the pharynx. This often occurs when iodized

oil is placed in the mouth for fluoroscopic examination of the esophagus.

2. A large quantity of contrast substance in the esophagus will obscure the narrow tract of the fistula. Children are usually examined in the supine position; however, this type of fistula arising from the anterior portion of the esophagus is most easily filled in the prone position.

ACQUIRED TRACHEOESOPHAGEAL FISTULA

After surgical repair of tracheoesophageal fistula with or without atresia of the esophagus, the fistula may recur. Acquired tracheoesophageal fistula should always be kept in mind in evaluation of the postoperative patient who continues to have feeding difficulty or recurrent aspiration pneumonitis. One of our postoperative patients was examined by bronchoscopy and esophagoscopy several times without visualization of a fistula which was later easily demonstrated at autopsy. We have observed two such recurrences in recent years.

Fig. 3.—X-ray film showing the characteristic defect in the posterior wall of the esophagus due to the presence of an anomalous right subclavian artery.

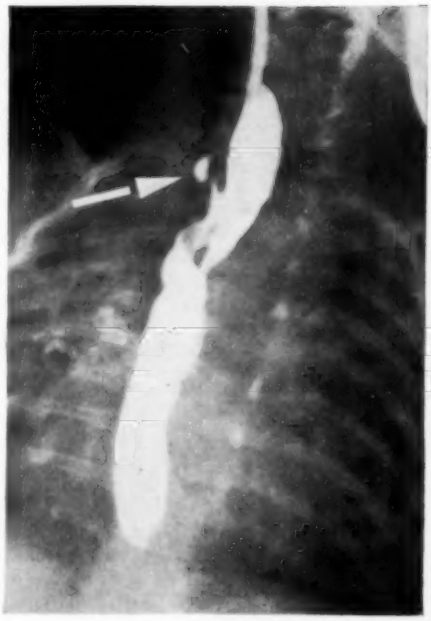


Fig. 4.—This film demonstrates the filling defect of an aberrant right subclavian artery, and, slightly above, the iodized oil outlines the tract of the fistula curving upward to enter the trachea and is seen spreading over the posterior wall of the trachea.

SUMMARY

The 16th case of tracheoesophageal fistula without esophageal atresia corrected surgically is reported.

Characteristic symptoms are due to aspiration of liquid into the lungs, with choking, coughing, and cyanosis causing recurrent pneumonitis and inanition.

Diagnosis was proved by injection of iodized oil into the midesophagus through a catheter and roentgen visualization of the escape of oil into the lungs through the tracheoesophageal fistula with the patient in the prone position.

This radiological procedure should be attempted whenever repeated aspiration of ingested fluids occurs and the cause cannot be satisfactorily explained. The lesion will frequently be missed by routine roentgen examination.

The fistula tapers as it curves upward and forward, so that its roentgen appearance simulates the spout of a teapot.

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Abstracts from Current Literature

Diseases of Blood, Heart and Blood Vessels, and Spleen

THE CLINICAL DIAGNOSIS OF AORTIC VALVULAR STENOSIS. H. ELSBACH, Nederl. tijdschr. geneesk. **98**:1478 (May 29) 1954.

Aortic valvular stenosis is a rather frequent heart disease. Within one year 80 new cases have been seen in the cardiological department of the University Hospital of Leyden. In 50% of these cases the aortic valvular lesion was associated with other cardiac anomalies, most frequently a mitral valvular disease. In a number of cases the lesion was associated with a coarctation of the aorta. This association is due to the frequent combination of coarctation with bicuspid aortic valves, which are very prone to infective endocarditis. The author noted the greatest number of cases in males. Calcification occurred most frequently above 60 years of age. Above this age the diagnosis can hardly be accepted if calcifications are not demonstrable. The lesion can be caused by rheumatic endocarditis, a sclerosing process, or a combination of them. Some authors do not accept a congenital form. A subvalvular aortic stenosis is a rare anomaly. Typical complaints are dyspnea, vertigo, syncope, and angina of effort. The angina of effort may be due to compression of the coronary arteries during systole. Sudden death is mentioned in 10%-20%. Physical signs are (1) a systolic murmur and thrill in the second right intercostal space and on Erb's point, (2) the carotid shudder, a murmur audible over the vessels of the neck, which resembles a gallop rhythm, (3) a diastolic murmur, heard in half of the cases. A pulsus tardus and a small pulse pressure are not essential features for the diagnosis.

X-ray findings were as follows: Calcifications are frequent at a high age, but are often seen at middle age. They can be demonstrated by screening in the right oblique position. The hypertrophied left ventricle can be judged in the left oblique position. The electrocardiogram shows a left preponderance. The general course of the disease is slow and insidiously progressive. The lesion gives rise to complaints in increasing frequency over the age of 50 years. In view of the operability of this anomaly in recent years, an early diagnosis is more and more important.

VAN CREVELD, Amsterdam.

GAMMAGLOBULINOPENIA. J. C. M. VERSCHURE, Nederl. tijdschr. geneesk. **98**:2805 (Oct. 2) 1954.

In several diseases an abnormal γ-globulin content in the serum has been noted. The change in the serum proteins seen most frequently is a fall of the albumin level and a rise of the γ-globulin level. The rise of the γ-globulin content is not associated with a rise of antibodies.

Protein spectrums were determined by paper electrophoresis in 2300 patients. The γ-globulin content of the serum was diminished in 15 patients. Four of these patients suffered from β-plasmocytoma, two had cancer metastases, three patients suffered from nephritis, two were emaciated by malnutrition, one suffered from generalized lupus erythematodes, one patient was emaciated, and in one patient no diagnosis was established. In only one case a severe acute infection was present. In this latter patient the γ-globulin content of the serum rose to normal values after recovery.

No correlation was observed between gammaglobulinopenia and tendency to infections. However, in groups of patients suffering from aforementioned diseases, infections are known to occur frequently.

VAN CREVELD, Amsterdam.

OBSTRUCTIVE JAUNDICE IN INFANTS WITH NORMAL BILIARY TREE. RUTH C. HARRIS, DOROTHY H. ANDERSEN, and RICHARD L. DAY, Pediatrics **13**:293 (April 1) 1954.

Of 50 infants with persistent signs of biliary obstruction, not atresia, whom the authors have seen in the past sevent years, 16 had preceding hemolytic disease from ABO or Rh incompatibility and 3 had acquired hemolytic anemia. One infant probably had serum hepatitis, and 30 others had hepatitis of unknown etiology. All had patent external biliary tracts.

Clinically, thse patients had jaundice, light stools, and dark urine. All appeared in a good state of nutrition except those with hepatitis of unknown cause. The results of laboratory studies

have been similar in these patients and have included a high direct serum bilirubin, usually negative cephalin flocculation, frequently elevated zinc sulfate turbidity, and low cholesterol esters. The urine urobilin may be absent or increased in amount.

Histologic studies of liver have shown the presence of multinucleated giant liver cells, much myelopoiesis and erythropoiesis, plugging of bile canaliculi, and mild bile-duct proliferation. Large amounts of yellow pigment have been found within the liver cells, but this pigment has not taken the usual iron stains. Livers from patients with hepatitis of unknown etiology have shown more evidence of inflammation, cell necrosis, and portal fibrosis than the other infants.

Pertinent laboratory studies to help differentiate these cases from cases of biliary atresia have included determinations of serum bilirubin, zinc sulfate turbidity, cholesterol and cholesterol esters, and urine urobilin. Studies of maternal and infant blood factors and a search for evidence of agglutination and increased production of erythrocytes are also important. Tests found not to be useful in differentiation are cholesterol esterase, alkaline phosphatase, and prothrombin time.

If diagnosis is impossible from clinical and laboratory information, exploration of the biliary tract with liver biopsy and Diodrast cholangiography may be ncessary.This procedure should be delayed until an adequate period of observation has elapsed and until the infant is over 4 months of age. Such a delay may result in spontaneous clearing up of the jaundice, with complete recovery.

FROM THE AUTHORS' SUMMARY

RETROPERITONEAL MYXOLIPOMA: REPORT OF CASE IN A CHILD SEVEN YEARS OF AGE. V. CARVALHO PINTO, A. GOMES MATTOS, E. PIMENTA, R. VILHENA MORSES, and P. ALTENFELDER, Pediatrics **14**:11 (July) 1954.

A case of a fatty tumor of the retroperitoneal space, with the histologic diagnosis of myxolipoma, is presented. The boy was 7 years of age and weighed 24.2 kg.; the tumor weighed 12.8 kg., that is, more than half the child's weight.

The clinical history suggests that the tumor appeared at the age of 1½ years and developed without any complications of the renal and intestinal functions. There was predominance of the myxomatous tissue, and the removal of the whole tumor was possible. It was located between the mesenteric leaves, and for its removal, 5 cm. of the ileum had to be resected. The complete extirpation was performed, and the child is in very good physical condition six months after the operation.

FROM THE AUTHORS' SUMMARY

RESECTION OF ESOPHAGEAL VARICES. EDUARDO ECHEVERRÍA, Pediatrics **14**:45 (July) 1954.

Brief considerations are made of the incidence, symptomatology, and endoscopic and radiologic diagnosis of esophageal varices. Mention is made of different treatments advocated. Three cases in children are described; two of the children had liver cirrhosis and one had blocking of the portal vein and chronic congestive splenomegaly with profuse hematemesis by varices. Splenectomy and splenorenal anastomosis were practiced without results in two cases. In view of the persistence of hematemesis, an ample thoracotomy was performed, followed by longitudinal incision of the esophagus; this brought into view the various columns, which were then resected. The esophagus was sutured in two layers. The postoperative course was satisfactory, and in the esophagoscopic control done two years afterward in two of the cases shown there has been no reproduction of varices. The third patient is still under observation.

FROM THE AUTHOR'S SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

PATHOGENESIS OF DECOMPOSITION (MARASMUS). E. KERPEL-FRONIUS, F. VARGA, and K. KUN, Ann. paediat. **183**:26 (July) 1954.

The following findings were made with regard to the "terminal" stages in marasmus. "Toxic traits" were found in cases of anoxia due to anhydremia. If the O_2 requirements were greatly reduced by inanition and hypothermia, the vita minima of hibernation was produced. Marked hypothermia is frequent because inefficient chemical heat regulation adds to the increased heat loss. Respiratory disturbances with apnea are frequently caused by hypoglycemia, which is proved by the fact that the oxygen consumption of the brain is greatly reduced while the symptoms can be influenced by giving sugar.

The knowledge of the physiopathological happenings made possible the treatment of cases formerly considered to be "terminal." It is of etiologic and prophylactic importance that since the introduction of scrupulous dyspepsia coli prophylaxis and of treatment with chloramphenicol and transfusions in all marantic children with precipitate weight losses decomposition was reduced to one-quarter of the former number, while mortality in the hospital occurred only in half the cases.

FROM THE AUTHORS' SUMMARY

PATHOLOGY OF HEMOLYTIC BACTERIACEAE. KRUNA TOMIC-KAROVIC, Ann. paediat. **183**:119 (Aug.) 1954.

The problem of hemolytic enterobacteriaceae is discussed. Hemolytic Enterobacteriaceae have been isolated from the bile, the gastric juice, the contents of the duodenum, the feces, the urine, pus derived from the skin, the maxillary sinus, the middle ear, the nasal secretion, throat and bronchial swabs, and blood cultures. Cases of enterocolitis and two cases of infection of the uropoietic system which were caused by these microbes are described.

The children presented the clinical picture of typhoid or of bacillary or amebic dysentery. They had 7 to 10 loose stools a day, containing blood and mucus; in one case the manifestations were like melena. Dehydration developed to a more or less marked degree on account of the intoxication, and in a few cases septicemia or thrombophlebitis of the extremities ensued. At the postmortem examination micropolyadenitis was found in two cases. The clinical picture was conditioned by the thermolabile neurotoxin and the thermostabile enterotoxin, as well as by the toxins responsible for hemolysis and necrosis.

FROM THE AUTHOR'S SUMMARY.

HEPATIC CHANGES IN NUTRITIONAL DISTURBANCES: THE LIVER IN DYSTROPHY. ARTURO J. ABALLI, Rev. cubana pediat. **26**:431 (July) 1954.

The authors studied the condition of the liver in a series of 35 cases of nonspecific infantile malnutrition. Of these cases, 16 infants were over 9 months of age and 19 younger than 9 months.

The incidence and intensity of the liver lesions revealed by biopsy were not nearly as severe as in the lesions found in cases of nutritional edema and pellagra or kwashiorkor.

Nearly one-half (17 cases) of these malnourished infants had normal livers, and the majority of the remaining 18 infants had relatively slight pathological lesions. Mild degrees of fatty infiltration and protein depletion images were the usual pathological findings.

The incidence of liver pathology was especially low in infants under 9 months; 68.4% of these infants had normal livers.

When one compares these findings with those in cases of nutritional edema or pellagra, it appears that fatty infiltration and protein depletion are probably due to specific nutritional deficiencies. These deficiencies must be present through fairly long periods; probably the young infant has reserves of these substances offering protection against hepatic lesions of a purely nutritional origin.

Infections play an important part in the etiology of the fatty infiltration encountered in many conditions at any age.

In infants under 9 months every patient showing such lesions had an active infection; after that age the role played by infection was less constant. Thus, purely nutritional lesions tend to occur, as a rule, in older infants.

Series of liver function tests performed in these cases have been quite satisfactory in detecting the slight liver involvement present, provided the correct selection is made.

The Bromsulphalein test has been the most accurate, and the epinephrine test appears to be the most sensitive.

The best information is obtained by combining the Bromsulphalein, the Takata-Ara, the cephalin-cholesterol flocculation, and the epinephrine tests and the determination of the serum proteins. Accurate palpation of the liver also offers a certain degree of orientation. With this combination it is usually possible to detect even the presence of mild hepatic lesions.

It two cases it was shown that in certain early phases of hepatic insufficiency glycogenolysis may be abnormal before there is any alteration of glycogenesis.

Control of infections is of vital importance in order to eliminate the existent liver pathological condition completely.

In malnourished infants the use of synthetic vitamins of the B-complex should always be accompanied by the administration of lipotropic factors or crude liver extract.

FROM THE AUTHOR'S SUMMARY.

CASE OF ENCEPHALOPATHY FROM ENTERITIS IN AN INFANT. W. KRAMER, Maandschr. kindergeneesk. **22**:223 (July) 1954.

Severe gastroenteritis in an 8-month-old child was followed by convulsions and a hemiplegia. She died on the 10th day of the illness, owing to involvement of the central nervous system. At postmortem examination an encephalopathy was found which was characterized by toxic alterations of the blood vessels and of the nerve parenchyma. Signs of inflammation were lacking. Problems concerning the pathogenesis are discussed.

FROM THE AUTHOR'S SUMMARY.

ROLE OF CONSERVATIVE TREATMENT IN MANAGEMENT OF INTUSSUSCEPTION. R. B. ZACHARY, Maandschr. kindergeneesk. **22**:310 (Sept.) 1954.

With selection, conservative treatment can be successful in a high proportion of cases of intussusception. If the technique is restricted to those children with a history of the condition for less than 24 hours, there is no danger. The procedure must be in responsible hands, and the child should be under the direct care of the surgeon, who may have to operate.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

INFECTIOUS MONONUCLEOSIS AND GUILLAIN-BARRÉ SYNDROME: REPORT OF THREE CASES. M. RAFTERY, E. E. SCHUMACHER JR., G. O. GRAIN, and E. L. QUINN, A. M. A. Arch. Int. Med. **93**:246 (Feb.) 1954.

The occurrence of nervous system involvement in infectious mononucleosis is stressed. The authors report three such cases in which the neurologic manifestations took the form of an acute polyradiculoneuritis. Infectious mononucleosis is not invariably a benign disease, and nervous system involvement ranks high among the causes of death. Spontaneous rupture of the spleen and myocarditis account for the majority of the other fatalities that have been reported.

JONES, Chicago.

CHLORPROMAZINE AS A THERAPEUTIC AGENT IN CLINICAL MEDICINE. JOHN H. MOYER, VERNON KINROSS-WRIGHT, and R. MILTON FINNEY, A. M. A. Arch. Int. Med. **95**:202 (Feb.) 1955.

The authors summarize their rather extensive experience with chlorpromazine (Thorazine); they have found it to have wide application in neuropsychiatry. With the help of this drug they were able to bring about total disappearance of symptoms in both acute and chronic cases of schizophrenia for as long as one year. It is also effective as an antiemetic agent. They had experience with a small group of children with various behavioral disturbances. These children all experienced marked benefit. The ages of these children ranged from 2-13 years. It was helpful in hyperactivity associated with brain damage, such as with Sydenham's chorea. The drug was also found to have some anticonvulsant activity. It is noteworthy that the children appeared to tolerate adult doses with fewer side-effects than adults.

JONES, Chicago.

PLASTIC SURGICAL REPAIR OF LUMBAR MYELOMENINGOCELE. PAUL W. GREELY, ERIC OLDBERG, and JOHN W. CURTIN, Ann. Surg. **142**:552-559 (Oct.) 1955.

A new method of skin-flap closure over lumbar myelomeningoceles is presented. The authors had no failures. to date. There has been no postoperative leakage of spinal fluid, nor has there been any increase in the degree of hydrocephalus.

BANTIN, Omaha.

ELECTROENCEPHALOGRAM IN EPILEPSY. HENRY W. NEWMAN, California Med. **80**:59 (Feb.) 1954.

In light of the considerable divergence of opinion among various investigators regarding the incidence of electroencephalographic abnormality in patients with convulsive disorders, the author made a study of his own records of 430 patients with a diagnosis of epilepsy. In 122 patients the seizures were symptomatic, in the remainder idiopathic, and the over-all incidence

of electroencephalographic abnormality was little different in the two groups. In the whole series 64.9% showed abnormal tracings, while in those under 16 years of age the incidence was 71.8%. The highest incidence was in patients in whom seizures had begun when they were between 10 and 15 years of age and in those with a duration of seizures from 5 to 10 years. Of patients with clinical petit mal, 76% had abnormal records, but only 34.6% showed petit mal complexes. Lateralized or focal abnormality was three times as frequent in the symptomatic as in the idiopathic group.

PRYOR, Redwood City, Calif.

NUVARONE (3-METHYL-5-PHENYLHYDANTOIN) IN THE TREATMENT OF EPILEPSY. J. H. TATERKA and C. B. THOMPSON, Dis. Nerv. System **14**:108 (April) 1953.

The authors report a clinical trial, in 91 patients, of the antiepileptic substance Nuvarone, which has previously been described as highly effective against induced seizures in experimental animals. Twenty-five patients received the new medication alone; sixty-six had it combined with another anticonvulsant. Seventy-three had had prior unsuccessful therapy with one or several drugs. The dosage of Nuvarone varied from 1.0 to 3.0 gm. a day, in divided (0.5 gm.) amounts. The response was deemed "fair" (attacks reduced by 35% to 75%) or "good" (attacks reduced by 75% to 100%) in 82 cases (90%). Grand mal and psychomotor illness were benefited in about equal proportions. Petit mal spells were not in any way affected in patients suffering from mild petit mal and grand mal disease, though the latter component was improved in all. A single case of myoclonus epilepsy was not controlled. Patients with paroxysmal electroencephalograms and diagnoses of migraine and impulsive behavior disorder showed some betterment. No changes in brain wave patterns were noted while patients were taking Nuvarone. Side-effects, mostly mild and transitory, occurred in 19 cases (21%) and included rash, itching, drowsiness, restlessness, headache, abdominal pain, transient loss of taste, mild fever, leucopenia, leucocytosis, and ecchymoses. Though the blood reactions were not severe, they do point up the importance of routine laboratory examinations at regular intervals. Although essentially more toxic than Dilantin, Nuvarone frequently gives better results and has a definite place in the treatment of epilepsy. Unlike the former preparation, it does not appear to cause hypertrichosis, ataxia, or gum hyperplasia.

BEATON, Tucson, Ariz. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

FAMILIAL INCIDENCE OF CONGENITAL ANEURYSMS OF CEREBRAL ARTERIES. W. R. CHAMBERS, B. F. HARPER JR., and J. R. SIMPSON, J. A. M. A. **155**:358 (May 22) 1954.

It has now been widely accepted that intracranial aneurysms are of a congenital nature. The possibility that there may be a familial factor involved is suggested by this presentation of proved aneurysms in a father and son.

The father, a man of 52, suddenly became unresponsive, thick in speech, and drowsy and complained of a severe headache. Symptoms became progressively worse, and an angiogram revealed an aneurysm in the course of the left middle cerebral artery. At operation a large blood clot was evacuated from the temporal lobe; the aneurysm was found to have a wide, sessile base. Four months after operation the patient was almost ready to return to work. He was attending a speech therapy school in order to overcome a tendency to paraphasia.

Almost exactly two months after the onset of the father's attack, the 21-year-old son had a classic subarachnoid hemorrhage. Carotid angiography was done bilaterally, but no aneurysm could be demonstrated. His condition improved, and he was sent home. A second attack occurred about one month later. At this time his condition was so poor that further angiography was impossible. He died 24 hours after admission. Autopsy revealed an aneurysm of the anterior communicating artery. A blood clot extended down into the pedicle of the sac and evidently stoppered off the aneurysm in such a manner that the angiogram done on the first admission did not show a defect. A new rupture between this clot and the anterior communicating artery had occurred, and wide subarachnoid hemorrhage was present. The presence of a secondary anomaly, a posterior cerebral vessel arising directly from the internal carotid artery, would tend to support the congenital origin of these aneurysms.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

DISTURBANCES OF SENSATION IN CHILDREN WITH HEMIPLEGIA. J. P. M. TIZARD, RICHMOND S. PAINE, and BRONSON CROTHERS, J. A. M. A. **155**:628 (June 12) 1954.

One hundred six patients with hemiplegia were selected from a larger group with neurological defects, and reexamined. Of these, 50% were found to have sensory changes which had not been detected before. These sensory changes were slightly commoner in the acquired group and were proportional to the amount of skeletal "undergrowth." Stereognosis, two-point discrimination and position, and passive motion senses were most frequently affected. Next, touch and pain were affected, and least of all temperature. Homonymous hemianopsia was found in 25%.

KIMBALL, Evanston, Ill.

ASSOCIATION OF MATERNAL AND FETAL FACTORS WITH THE DEVELOPMENT OF EPILEPSY. A. M. LILIENFELD and B. PASAMANICK, J. A. M. A. **155**:719 (June 19) 1954.

The prenatal and paranatal records of 564 epileptic children born in Baltimore between 1935 and 1952 showed significantly more complications of pregnancy and delivery, prematurity, and abnormal neonatal conditions than a similar number of matched controls. These abnormalities were just as frequent among epileptic children whose parents had epilepsy as among those whose parents did not. These epidemiological findings throw some light on the etiology of epilepsy and raise doubts as to the genetic basis of convulsive disorders.

The pattern of factors, such as complications of pregnancy, prematurity, and neonatal abnormalities, that appear to be associated with epilepsy is similar to that previously found to be associated with cerebral palsy, stillbirths, and neonatal deaths. In a previous paper by Lillienfeld and associates, it was postulated that there exists a continuum of reproduction casualty comprising a lethal component consisting of stillbirths, neonatal deaths, and a sublethal component of cerebral palsy. The results of the present study suggest that this sublethal component should also include epilepsy. This observation, together with the fact that approximaely one-third of persons with cerebral palsy have convulsive seizures, suggests that cerebral palsy may be a result of a severer type of brain damage than is epilepsy. The results are sufficiently suggestive to warrant the continuance of similar studies concerning other possible components of this continuum. They also warrant serious consideration to the possibilities of establishing concurrent studies in which a group of infants classified by these maternal and fetal factors could be followed so that one can actually measure the attendant risks of various neurological conditions associated with these maternal and fetal factors.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

INTRASPINAL TUMORS IN CHILDREN. H. J. SVIEN and H. M. KEITH, J. A. M. A. **155**:959 (July 10) 1954.

This report is based on a review of the clinical records in 41 cases of intraspinal tumor in which the patients were less than 15 years of age. Svien and Keith found that in the majority of cases of intraspinal tumor in children the neoplasm arises from the spinal cord or its envelopes. In 27 (65.9%) of the 41 cases the tumor was of this type. In 9 of the 41 cases the tumor arose in contiguous tissues. In 2 of the 41 cases the intraspinal tumor was a metastatic lesion. The tumor was of the lymphoma type in 2 of the 41 cases.

In reviewing the results of treatment, the authors note that in 14 (34.1%) of the 41 cases, that is, in 8 cases of neurofibroma, 1 case of extradural lipoma, 2 cases of ependymoma of the filum terminale, 2 cases of arachnoid cyst, and 1 case of giant-cell tumor, it could be anticipated that surgical removal of the tumor would result in a cure provided the operation was performed before the tumor had caused irreparable injury of the spinal cord. In 14 of the remaining 27 cases, decompression of the spinal cord or cauda equina could be expected to relieve the symptoms for several months to several years provided the operation was performed before the spinal cord had been injured seriously. The remaining 13 cases of intramedullary tumors of the spinal cord consisted of 6 cases of glioma, 1 case of racemose angioma, 1 case of hemangioendothelioma, and 5 cases of lipoma. If partial removal of the tumor is possible, it sometimes will result in prolonged benefit.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PROTRUDED LUMBAR INTERVERTEBRAL DISKS IN CHILDREN. J. H. WEBB and R. L. KENNEDY, J. A. M. A. **154**:1153 (April 3) 1954.

Of approximately 6500 patients who were operated on for protruded lumbar intervertebral disks at the Mayo Clinic, only 5 (0.077%) were in the period of childhood (less than 16 years of age). The clinical and pathological features in these five cases do not differ significantly from those in adults who have similar lesions. A history of trauma that could be related to the onset of symptoms was obtained in three of the five cases. As in adults, the physical findings varied from minimal limitation of motion of the back to severe spasm of the erector spinal muscles, changes in reflexes, and neurologic defects.

Multiple protrusions were present in one case, namely, a midline protrusion at the fourth lumbar interspace and a lateral protrusion at the lumbosacral interspace. The protrusions in three of the four remaining cases were at the fourth lumbar interspace. Of these, two were midline in type. In the remaining case, a midline protrusion was present at the lumbosacral interspace. Here, too, these cases parallel the findings in adult patients.

Protruded intervertebral disks are rarely encountered in children, as this study shows. However, the authors point out that the occurrence of low backache and sciatic pain in a child should arouse suspicion of the possible presence of a protruded lumbar intervertebral disk. If other causes of these symptoms can be excluded, myelography and removal of the lesion should be considered, after a thorough trial of conservative therapy has failed to provide relief. All five patients experienced good results from surgical treatment.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

RECENT ADVANCES IN STUDIES OF VIRUS INFECTIONS OF THE NERVOUS SYSTEM. HERMAN C. MASON, Illinois M. J. **105**:72-76 (Feb.) 1954.

This article is a rather comprehensive review of recent advances in virus identification. It includes so much detailed information that it can hardly be abstracted adequately. The advances, as Mason points out, are based upon serological, immunological, and tissue-culture developments.

BARBOUR, Peoria, Ill.

ACQUIRED EPILEPSY—A STUDY OF 535 CASES. B. SMITH, G. C. ROBINSON, and W. G. LENNOX, Neurology **4**:19 (Jan.) 1954.

This study of 535 noninstitutionalized persons of various ages and economic statuses emphasizes the wide diversity of conditions, both genetic and acquired, which either alone or in combination may result in some of the various manifestations of epilepsy.

The authors reviewed the records of 1648 patients with a diagnosis of epilepsy. Of these, 535, or 32.4%, gave evidence of organic lesion of the brain acquired prior to the person's first seizure. In 52% the evidence for the pathologic change was believed conclusive; in 48%, only probable. Of the 535 patients 69% were private and 31% clinic patients, the latter being adolescent or younger.

Ninety per cent of patients had the first seizure before the age of 20; twenty-four per cent had a positive family history of epilepsy. Evidence for a cerebral lesion was furnished in largest proportion, 88%, by the patient's past history, with the electroencephalogram, description of seizures, neurologic examination, and pneumoencephalogram following in order of importance.

The causes of pathologic change were as follows: prenatal, 13.3%; natal conditions, 30.1%; postnatal trauma, 20.7%; injections, 17.2%; other conditions, 6.4%; unassigned, 12.3%.

Data studied with respect to the patient's age at the first seizure showed a progressive decline of paranatal mishaps and progressive increase of postnatal traumatic conditions with increasing age. Nearly one-half of the patients, 46%, had the initial seizure within 12 months after the first etiologic event. In 12% epilepsy did not arise until 10 years or more later. The time interval separating etiology and epilepsy was shorter for postnatal trauma and infections than for paranatal conditions.

The authors point out that the distribution of causes differs radically from a previous series of older patients.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CALCIFICATION OF THE INTERVERTEBRAL DISKS IN CHILDHOOD. F. N. SILVERMAN, Radiology **62**:801 (June) 1954.

Calcification may occur in the nucleus pulposus or in the annulus fibrosus or in both. It occurs also in the cartilaginous plates of the vertebral bodies, but this type has not been observed in children. Calcification in the annulus fibrosus is much commoner at all ages than calcification in the nucleus pulposus and probably represents a degenerative change which is usually of little or no clinical significance. Alkaptonuric ochronosis can produce a generalized calcification of both the nucleus pulposus and the annulus fibrosus of many intervertebral discs. The deposits of homogentisic acid in the cartilage ultimately cause degeneration of the cartilage, with clinical and roentgenologic manifestations of arthritis in addition to the calcification.

A third type of calcification occurs in the nucleus pulposus only. Its cause, whether or not it produces or is accompanied by symptoms, and its permanence are unsettled problems. Weens has described a calcification of the nucleus pulposus which occurs in childhood, is associated with clinical symptoms, and is of a transient nature. Other authors have demonstrated obvious calcification of the nucleus pulposus in children which has later disappeared. The suggestion has been made that those cases in which calcification is present and is apparently accompanied by acute symptoms, such as pain and stiffness in the region of the spine involved, and in which the calcification later disappears are very similar to the disease variously known as peritendinitis calcarea, myotendinitis calcarea, or "bursitis." However, there are also asymptomatic calcifications of an occasional nucleus pulposus in children, some of which disappear and some of which remain for long periods of time.

Silverman reports case histories of seven children, varying in age from 5 months to 11 years, in whom calcifications of the nucleus pulposus were demonstrated roentgenologically. The finding was thought to be an incidental observation in five of the seven patients and was associated with symptoms in the region of the calcification in two.

WEILAND, Grove City, Pa. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MEASLES MENINGOENCEPHALOMYELITIS. W. F. TWINING MCMATH, Brit. M. J. **2**:789 (Oct. 2) 1954.

The protean character of measles meningoencephalitis and its tendency to occur in small groups are well illustrated in a series of 10 cases of the disease, 3 of which occurred in the preeruptive stage, encountered in a localized area of northwest London between September, 1951, and June, 1953. Analysis of these 10 cases, which Twining McMath briefly presents, failed to elucidate the pathogenesis, prophylaxis, or treatment of this complication. The author believes that failure of corticotropin to influence the course of the disease in two cases supports the hypothesis of a virus rather than an allergic etiology. There appeared to be no correlation between the incidence and severity of the disease and the character of the primary lesion. There was one death in the series. None of the nine patients who recovered had physical residua, but two of them showed mental deterioration.

ECHOLS, New Orleans [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE LOCALIZATION OF A CEREBRAL LESION BY ARTERIOGRAPHY IN THE CASE OF A CHILD WITH NEUROFIBROMATOSIS. P. MONTENOVESI, Clin. pediat. **36**:647 (Sept.) 1954.

A 3½-year-old boy showed the typical skin lesions of multiple neurofibromatosis. The child had signs of increased intracranial pressure and sexual precocity. An arteriogram showed abnormality in the area of the sylvian fissure on an x-ray film, with the head in the lateral position. A pneumoencephalogram showed elevation of the third ventricle. Two years later, involvement of the right optic nerve was apparent.

HIGGINS, Boston.

THE ELECTROENCEPHALOGRAM IN FEBRILE CONVULSIONS IN CHILDHOOD. L. PARDELLI and R. ARDITO, Riv. clin. pediat. **53**:233 (Oct.) 1954.

The authors checked up, among a large number of cases of paroxysmal syndromes in childhood, on 10 cases in which one or more paroxysmal signs occurred exclusively in diseases with fever.

The authors point out the importance of electroencephalographic findings (normal in these cases) and outline some etiologic and pathogenetic factors. They believe that, through clinical findings and electroencephalographic records, diagnosis and prognosis are likely to be correctly stated.

FROM THE AUTHORS' SUMMARY.

CRANIAL HYPERTENSION IN CHILDREN. J. S. PICAZA, A. VALDES RODRIGUEZ, and M. DIAZ PADRON, Rev. cubana pediat. **26**:687 (Nov.) 1954.

On the basis of the experience gained from 351 cases of increased intracranial pressure in children, the authors conclude from the analysis of the clinical symptomatology that in its evolution three different periods can be distinguished.

First Stage.—Early Decompensation: Manifested principally by tension of the fontanelles, vomiting, and headache. The most important factors in the evaluation of these symptoms are studied.

Second Stage.—Compensation: Characterized by the opening of the sutures and the enlargement of the cranial perimeter, with its secondary consequences. This period may be absent.

Third Stage.—Late Decompensation: Vomiting and headache reappear, and the differential syndromes of compression of the brain stem develop.

The different methods for solving these situations are described, and special emphasis is placed on the description of the decompressive cranial puncture. The general measures for the management of intracranial hypertension in children are given.

FROM THE AUTHORS' SUMMARY.

CONVULSIONS IN TREATMENT WITH ACTH AND CORTISONE. D. J. VAN ZAANE, Maandschr. kindergeneesk. **22**:210 (June) 1954.

A review is given of some cases described in the literature of convulsions during treatment with ACTH or cortisone. Another case is reported in a 7-year-old girl treated with ACTH. Blood chemistry, cerebrospinal fluid, and blood pressure remained normal. A direct action of ACTH seems the probable cause, and it is suggested that during prolonged treatment with any of these drugs an EEG should be made at intervals; treatment should be stopped as soon as slow or pointed waves occur.

FROM THE AUTHOR'S SUMMARY.

CEREBROSPINAL FLUID IN NORMAL INFANTS BORN AT TERM. H. J. G. WYERS and J. C. W. BAKKER, Maandschr. kindergeneesk. **22**:253-263, 1954.

The authors give a description of a series of investigations on the cerebrospinal fluid of 50 young infants born at term. All infants with cyanosis, Rh incompatibility, low birth weight, or abnormal reactions after birth were excluded. The fluid was tapped between 2 and 24 hours after birth.

Every investigated spinal fluid was xanthochromic, a few contained bilirubin. The great majority showed a protein content and colloidal reactions that would be regarded abnormal in adults. In every spinal fluid were found white blood cells, and the majority contained erythrocytes. Owing to the wide differences in the results it was not possible to determine what values should be normal for a newborn infant born at term. Three children born by primary Caesarean section showed same pictures as infants of vaginal delivery. From this may be concluded that not the birth trauma itself but other factors are cause of the cerebral spinal fluid picture found in infants. As probable factors the authors think of the low barrier between blood and spinal fluid.

VAN CREVELD, Amsterdam.

IS A STRICTLY HORIZONTAL POSITION NECESSARY AFTER LUMBAR PUNCTURE? A. VERJAAL and B. KRAFT, Nederl. tijdschr. geneesk. **98**:1493 (May) 1954.

In most hospitals patients are kept lying flat on their back for 24 hours after lumbar puncture, in order to prevent complaints after puncture. To determine the efficacy of this measure 200 consecutive patients undergoing lumbar puncture were divided alternately in two statistically equivalent groups of 100 each. The patients of one group were free to move and were permitted to keep their pillows. The patients of the other group were kept lying flat on their back for 24 hours. As the number of patients with complaints after puncture was the same in both groups, it does not appear to be indicated that patients should remain lying flat for 24 hours after lumbar puncture.

VAN CREVELD, Amsterdam.

Psychology and Psychiatry

READING DISABILITIES IN CHILDREN: A SYMPOSIUM. California Med. **83**:79-88 (Aug.) 1955.

Introduction.—Poor readers are a problem for ophthalmologists, pediatricians, psychiatrists, and educators because the problem may involve the eyes, ears, personality disorder or teaching method.

Ophthalmological Factors.—Reading disabilities may be generally classified as specific and nonspecific. The term specific reading disability is used for cases in which there is confusion in the recognition of language symbols, with reversals, inversions, omissions, substitutions, or other faulty interpretation.

Nonspecific reading disability is used to identify cases in which ocular abnormalities, low intelligence, emotional factors, or other factors prevent normal progress in learning to read.

The effect of moderate refractive errors has been grossly exaggerated. Except in cases of pronounced refractive errors, a child's power of focusing is sufficient to give adequate vision. Indeed, slight myopia may even be an advantage rather than a disadvantage in reading.

The presence of muscle imbalance or "crossed eyes" (provided there is normal vision in one eye) has little or no effect on reading ability, since vision in one eye is adequate for reading, and the image in the nonfixing eye is suppressed so that there is no confusion or "incoordination." Depth perception, variation in image size as seen by the two eyes, and eye movements have been ruled out as contributing causes.

Many children no longer learn the alphabet, as attested by the increased use of the illiterate "E" or kindergarten charts for vision testing. Bakwin said that 10% to 15% of public school pupils have some reading disability and that it is the major cause for school retardation.

A return to the earlier concepts of teaching is essential to these children. The earlier methods started with the alphabet, built this into combinations of simple sounds or syllables, then into words that were seen (visual), spoken (phonetic), heard (auditory), and written (kinesthetic). Some children need to hear the word as well as see it, to break it up into parts and say it, and to feel it by writing it.

Etiology and Emotional Factors.—There is no one cause for reading disability. There is no one etiological factor which is found uniformly in poor readers and is likewise uniformly absent in good readers. Children fail to learn to read for various reasons, and in each child the cause or combination of causative factors must be individually determined.

It is now well known that not all of the developmental aspects of a child progress necessarily at the same rate. There are individual differences in rates of nervous-system maturation, not only in general but in specific functions. One child who eventually rates in the same intellectual classification as another, for instance, may be slower to walk; another will be slower to talk; another will be slower to read.

Studies have shown that a higher percentage of children who are nonreaders than those who learn to read readily do show manifestations of confused cerebral dominance, such ambidexterity or learned right-handedness in a naturally left-handed person; or mixed cerebral dominance, such as is present when there is right-handedness and left-eyedness; or left-handedness and right-eyedness.

A specific and relatively poor visual memory is said to be another condition which handicaps some children in learning to read by the now widely used "sight" or "flash card" method of teaching reading. Experiment has shown that many if not most children learn to read most rapidly by learning to associate meanings with whole words. There are those, however, who do not learn by this method, or do so with great difficulty. Such children, like those who show evidences of strephosymbolia, learn more readily, at least at first, by utilizing their authority and kinesthetic avenues of learning. They learn to read best by the so-called "phonic system," learning the sounds of the letters and syllables so that they have a method of sounding out the word when the pronunciation and meaning is not otherwise obvious to them; also through tracing or copying, by learning the feel of the letter and syllable in relation to its sound as well as to its sight.

The Schools and the Methods of Teaching.—What persons who are not professionally concerned with education often do not recognize is that the school problem today is not the same as it was a generation ago. Twenty-five years ago the school was an institution which weeded out the inept and only retained those who could achieve in terms of certain set academic standards.

When today we have 98 out of every 100 pupils moving from the eighth grade into the ninth in contrast to former years when only one out of every two moved from the fourth grade into the fifth, we can readily see that the school is now tending to retain the great majority of school age population up until about the age of 16. This means that it has a much wider range of individual differences with which to deal. No longer do the children who formerly failed to learn to read stop school and go to work. They are by law required to remain within the school population.

Here are some of the factors with which the school has concerned itself and in which teachers of our schools have taken leadership: (1) development of real understanding of the reading process and of the developmental sequences in learning to read; (2) study of the methodology in the teaching of reading; (3) the recognition of the importance of providing a positive and constructive psychological atmosphere; (4) the encouragement of individual face-to-face guidance.

Corrective Measures.—Most children are ready to read by 6½ years of age. However, a substantial number are not ready until 7 or 8 years. In fact, it has been estimated that, in a typical school population, 25% to 30% of the children in the first grade are not ready for the regular reading program. On the other hand, there is the occasional child who is cheerfully and glibly ready to read at 5 years.

A basic consideration in the correction of reading problems involves the recognition of and provision for individual differences in reading.

Many methods for the teaching of reading have been developed. There are the so-called visual methods, whereby a child learns to recognize the configuration of a word. Phonics entails a system which enables a child to pronounce or identify a word by the sounds. Structural analysis teaches the child to break down the word into smaller units. Kinesthetic methods emphasize tracing and writing the word or phrase.

Applied to reading, then, it is apparent that a variety of learning methods provides a child with a variety of tools for recognizing words. He needs different methods of attack to serve different types of words.

It apepars that there is no prefabricated plan or panacea for all reading problems. The same prescription cannot be given to all children.

Summary.—In summarizing, certain common denominators stand out. The problem is not a new one, but rather an old one with poor public education and little progress over a period of years. The actual increase in numbers of poor readers, real or apparent, is difficult to establish, although it is agreed that it is probably real. It appears that the demands are greater today, that a higher value is placed upon reading skills, that reading skill is more necessary in the learning process and in society, and that failure to read well is now more apparent than once it was, since more students remain in school longer now.

The goal is to make it easier for all children to learn to read and to remove all possible obstacles as long as it is practical to do so and thus avoid the pitfalls that make such panel discussions as this necessary.

PRYOR, Redwood City, Calif.

STUDIES ON THE MECHANISM OF STIMULATION OF ACTH SECRETION WITH THE AID OF MORPHINE AS A BLOCKING AGENT. F. NORMAN BRIGGS and PAUL L. MUNSON, Endocrinology **57**:205-219 (Aug.) 1955.

The rapidity with which the pituitary can release adrenocorticotropic hormone (ACTH) in response to various stimuli suggests that the nervous system must play a role in regulating pituitary function.

A method for studying the role of the central nervous system is through the use of depressant drugs, and this report describes the effect of morphine on the pituitary-adrenal-cortical system.

It is demonstrated that morphine does not interfere directly with the response of the adrenal cortex to ACTH.

The results are interpreted in support of the hypothesis that the hypothalamus is an essential component of the mechanism of acute stimulation of ACTH secretion.

JACOBSEN, Buffalo.

COMPARATIVE STUDY OF SOME EFFECTS OF ADMINISTRATION OF DIHYDROTACHYSTEROL AND CALCIFEROL TO RATS. ROY V. TALMAGE and B. F. DODDS, Endocrinology **57**:236-242 (Aug.) 1955.

Dihydrotachysterol (Antitetanic Preparation 10) an irradiation product of ergosterol, has been used for many years as a substitute for parathyroid extract in human therapy. Its use has been based on its ability to maintain near normal serum calcium levels in cases of hypoparathyroidism without producing the toxic effects or refractoriness after prolonged administration, which often accompanies the use of parathyroid extract, but there has been some disagreement concerning the mode of action of dihydrotachysterol.

The experiments here reported are concerned chiefly with the influence of both dihydrotachysterol and calciferol on calcium and phosphate serum levels and on the progressive excretory changes of these two ions following parathyroidectomy.

It is concluded that the action of dihydrotachysterol in rats is restricted almost entirely to its ability to remove calcium and phosphate from bone.

JACOBSEN, Buffalo.

Diseases of Genitourinary Tract

INTERSTITIAL-CELL TUMORS OF THE TESTIS IN CHILDREN. FRANK A. POMER, RICHARD E. STILES, and JAMES H. GRAHAM, New England J. Med. **250**:233 (Feb. 11) 1954.

Interstitial cell tumors of the testis in children of prepubertal age are rare. To date only 15 cases are reported in the literature. The authors describe the interstitial cell, and the quantitative fluctuations of this issue throughout life are explained briefly.

The interstitial cells actively produce the male hormone, testosterone, from boyhood to late middle life, and hence are responsible for the characteristics of masculine sexuality. The 17-ketosteroids, urinary metabolites of androgen, are present in the urine of both normal males and females, originating in the testicular secretion chiefly, but derived in part from the adrenal cortex. Urinary androgenic steroid assays and partition may therefore be used as indicators of interstitial cell activity; but the fact that the interstitial cell also produces estrogen (and is the main source of estrogen in the male) makes urinary estrogen determination a more accurate and reliable indicator of interstitial cell function.

Interstitial cell tumors of the testis are usually benign, but occasionally metastasis has been reported. This may occur long after the removal of a tumor considered initially to be benign; hence a long follow-up is indicated.

Signs of precocious puberty consistently develop in children, and this state must be differentiated from that caused by other conditions, e. g., adrenocortical tumors, intracranial lesions, and certain familial endocrine disorders. The diagnosis of interstitial cell tumor is usually made through the palpation of a tumor in the testis in association with uncomplicated sexual precocity. All the cases reported have been treated by orchidectomy, and varying degrees of regression of the secondary sexual characteristics have been noted.

The pathology of these tumors is described and one case report given in detail.

WHEELOCK, Denver.

INDUCED RENAL HYPERCHLOREMIC ACIDOSIS. S. ISRAELS, G. E. DELORY, and BETH GOURLEY, Pediatrics **13**:64 (Jan.) 1954.

An infant without previous renal disease was given a carbonic anhydrase inhibitor (No. 6063). Following administration of the drug the serum alkali reserve fell, the serum chloride rose, and the urine became less acid. The "total carbon dioxide" excreted in the urine was also increased after administration of the inhibitor.

FROM THE AUTHORS' SUMMARY.

POTENTIAL VALUE OF SULFAGUANIDINE IN UROLOGY. J. W. INGALLS JR., Science **119**:191 (Feb. 5) 1954.

The author calls attention to the fact that sulfaguanidine, although poorly absorbed from the gut, is rapidly excreted in the urine. His data indicate that a urinary concentration of 100 to 200 mg. per 100 cc. is achieved after oral doses of 3 to 4 gm. in adults. No data are offered as to the bacteriostatic effect to be anticipated from these amounts for the common urologic pathogens.

FORBES, Rochester, N. Y.

TREATMENT OF NOCTURNAL ENURESIS WITH METHANTHELINE BROMIDE. JORGE PALMA ECKART, Rev. chil. pediat. **25**:26 (Jan.) 1954.

Six children, from 4 to 6 years of age, with nocturnal enuresis were treated with Banthine. All the patients showed a rapid and satisfactory response. With one exception the drug was fairly well tolerated.

FROM THE AUTHOR'S SUMMARY.

THERAPY OF NEPHROTIC SYNDROME IN CHILDHOOD. E. LORENZ, Wien. klin. Wchnschr. **66**: (Jan. 29) 1954.

Remarkable similarities in the effect of thiosemicarbazone (Conteben) with that of cortisone or ACTH in cases of acute polyarthritis prompted the use of this drug in the treatment of nine children, of whom four had primary nephrosis and three secondary nephrosis. One patient had amyloid nephrosis and one a mixed glomerular and tubular nephropathy. The drug is given by mouth in a dose of 1 to 3 mg. per kilogram of body weight daily. It seemed more advantageous to give the drug for 10- to 14-day periods. The diuretic effect is noted perhaps more promptly than with ACTH. In the further course the results of ACTH, cortisone, and thiosemicarbazone were about equal regarding the disappearance of edema. The dysproteinemia becomes normal later with all three drugs. Of the nine children, two were apparently cured. They had no more edema, and the protein picture of the serum was normal. With all three drugs the correction of the serum proteins takes more time to cure than does the edema. Two patients did not return for check; they probably did well. One patient with primary nephrosis died. It may be that recurrences are less frequent with thiosemicarbazone than with ACTH. The mechanism of the action of thiosemicarbazone is discussed.

AMBERG, Rochester, Minn.

Diseases of Ductless Glands; Endocrinology

ON THE THERAPEUTIC VALUE OF ACTH AND CORTISONE IN EXPERIMENTAL BURNS. W. H. A. SCHOTTLER, Endocrinology **57**:445-449 (Oct.) 1955.

Medication with adrenocorticotropic hormone and cortisone has been recommended for a great variety of pathological conditions, including severe burns, where even the exclusive use of such drugs has been advocated. However, a critical survey of the clinical reports on which these claims are based reveals that in most of the cases hitherto described either the severity of the thermal injury was not convincingly established by the usual criteria of hypotension, hemoconcentration, and reduction of urinary output or the concomitant application of other treatments, as, for instance, infusion of large volumes of plasma, confounded the issue. To test the value of such therapy under controlled experimental conditions the following experiments were carried out.

Mice were scalded in hot water and afterwards treated with ACTH, cortisone or a mixture of both hormones in doses ranging from 0.5 to 25.0 mg/kg. In a total of 600 animals including controls, no beneficial effect of hormone therapy was observed. Under the conditions of the experiment, cortisone proved to be contraindicated for the treatment of burns because it significantly enhanced mortality.

JACOBSEN, Buffalo.

HISTOLOGICAL OBSERVATIONS IN THE ZONA GLOMERULOSA OF THE RAT ADRENAL CORTEX FOLLOWING ADMINISTRATION OF CORTICOTROPIN PREPARATIONS. BERNARD C. WEXLER and ARTHUR P. RINFRET, Endocrinology **57**:608-620 (Nov.) 1955.

The zona glomerulosa of the adrenal gland of the hypophysectomized rat maintains its morphological integrity and a readily demonstrable lipid content, while the zonae fasciculata and reticularis atrophy. These observations have suggested that the zona glomerulosa of the rat adrenal cortex is independent of the pituitary gland. The experiments reported were designed to test a hypothesis based on observations incidental to earlier experimentation, i. e., lipid mobility in the zona glomerulosa of the rat is subject, in part at least, to pituitary control.

The results demonstrate an action by material of pituitary origin on the zona glomerulosa of the rat adrenal cortex.

JACOBSEN, Buffalo.

DEVELOPMENT OF GOITERS IN CRETINS WITHOUT IODINE DEFICIENCY: HYPOTHYROIDISM DUE TO APPARENT INABILITY OF THE THYROID GLAND TO SYNTHESIZE HORMONE. LAWSON WILKINS, GEORGE W. CLAYTON, and MORGAN BERTHRONG, Pediatrics **13**:235 (March) 1954.

The authors have reported a series of four cases of congenital cretinism in which the thyroid gland was present and capable of taking up iodine. The patient lived in regions where there is an abundance of iodine, and there is no history of the intake of excessive goitrogens. In the two younger patients, the thyroid gland was not enlarged. The two older children, however, developed goiters at the respective ages of 6 years and 8½ years. The goiter of the oldest child showed generalized hyperplasia of a high degree and, in addition, contained encapsulated nodules resembling adenomas or carcinomas. The case was similar to those cases described by Stanbury and by others.

There is a strong tendency for this type of hypothyroidism to be familial. It is probably due to an inborn defect in the ability of the thyroid gland to convert inorganic iodine into thyroid hormone. The precise step at which the path of synthesis is defective is not known, and all cases may not be the same. In early life, the gland may not be enlarged. If the hypothyroidism is not adequately treated, a goiter with hyperplastic and neoplastic changes is prone to develop later, probably because of the compensatory secretion of large amounts of pituitary thyrotropin. In spite of the histologic appearance of carcinoma, malignant spread has not been reported. Nor has exophthalmos been observed.

This type of hypothyroidism was described by Osler in 1897 and should be recognized as distinct from sporadic athyrotic cretinism or endemic (iodine-deficient) cretinism. Although comparatively uncommon, its incidence may be higher than suspected. In the absence of goiter, the diagnosis can be made only by the study of the uptake of I^{131}. The importance of adequate and continuous treatment with thyroid substance in the prevention of goiter is obvious.

FROM THE AUTHORS' SUMMARY.

EARLY DIAGNOSIS AND EARLY THERAPY IN CONGENITAL CRETINISM. Y. AKERREN, Arch. Dis. Childhood **30**:254 (June) 1955.

There is an obvious coincidence between congenital cretinism and icterus neonatorum of excessive duration. In babies with congenital cretinism who come under observation before the age of 3 months, icterus seems to be very frequent.

The knowledge of this syndrome must be assumed to be of practical importance for the early diagnosis of congenital cretinism. In cases of icterus neonatorum of excessive duration careful observation and examination must be performed until the diagnosis can either be made or excluded.

In cases of severe congenital cretinism, early treatment, i. e., beginning before the approximate age of 5 months, gives a much greater chance of obtaining a favorable mental prognosis than if the treatment is started later.

As an early diagnosis of congenital cretinism is a reason for early adequate therapy, the knowledge of the congenital cretinism-icterus-neonatorum syndrome is of value from the therapeutic and prognostic points of view.

KELLY, Milwaukee.

RICKETS WITH ALKALINE PHOSPHATASE DEFICIENCY: AN OSTEOBLASTIC DYSPLASIA. BERNARD SCHLESINGER, JOSEPH LUDER, and MARTIN BODIAN, Arch. Dis. Childhood **30**:265 (June) 1955.

Three cases of a rare bone disorder are described in which calcification is defective. This has been proved to be associated with deficient production of alkaline phosphatase. It is suggested that the primary fault may be in osteoblast formation and that it would not be unreasonable to call this condition osteoblastic dysostosis. One of the main factors in the diagnosis is the discovery of hypophosphatasemia, but hypercalcemia is also present and may result in renal damage and nitrogen retention. This can prove fatal, but in less severe cases recovery can be expected and calcification of the affected bones ultimately takes place.

KELLY, Milwaukee.

DIABETES MELLITUS IN AN INFANT AGED THIRTY-NINE DAYS. B. GANNS, Proc. Roy. Soc. Med. **47**:132 (Feb.) 1954.

Diabetes occurring in a 39-day-old infant is described and treatment outlined.

MCGUIGAN, Evanston, Ill.

THERAPY OF CORTICO-ADRENAL-GENITAL SYNDROME OF THE ADDISON TYPE. E. SCHWARZ-TIENE, Ann. itali. pediat. **7**:179 (Aug.) 1954.

Pathogenesis and symptoms of the adrenal-genital syndrome with Addison-like clinical picture are discussed. The hormonal treatment of this singular endocrine syndrome of the infant is described.

FROM THE AUTHOR'S SUMMARY.

LONG-ACTING INSULINS IN MELLITUS OF CHILDREN. H. SPIESS, Deutsche med. Wchnschr. **80**: 1170-1172 (Aug. 19) 1955.

Insulin "Lente" and "Long" have been used in the treatment of 21 children 5-13 years of age with diabetes mellitus. The diet contained 1-3 gm. of protein, 1-2 gm. of fat, and 4-7 gm. of carbohydrates per kilogram per day, according to age. Some local reactions at the site of injection have to be reckoned with. The treatment with long-acting insulin should be preceded with short-acting insulin.

AMBERG, Rochester, Minn.

PSEUDOPUBERTAS PRAECOX. C. HOOFT, J. BEKAERT, and A. BLANCQUAERT, Maandschr. kindergeneesk. **22**:127 (April) 1954.

For more than one month an ointment containing diethylstilbestrol was regularly applied to the vulva of a 6-year-old girl. Shortly after the beginning of this "treatment," swelling of the breasts and pigmentation of the nipple were observed.

The treatment was stopped when vaginal bleeding occurred.

Normal quantities of gonadotropins, 17-ketosteroids, and 11-oxysteroids were found in the urine. There was an increased excretion of estrogen, which decreased in the following weeks (less than 10 units per 24 hours after one month).

No further hemorrhage occurred, and the glandular tissue of the mammae regressed.

The cause of this pseudopubertas praecox might have been determined with certainty if the diethylstilbestrol and the glucuronide content of the urine had been estimated.

FROM THE AUTHORS' SUMMARY.

EPITHELIOMA OF UNDESCENDED THYMUS IN A CHILD. W. P. PIRKEY, A. M. A. Arch. Otolaryng. **59**:237 (Feb.) 1954.

A case of the epithelial type of thymoma in an 11-year-old Negro girl is presented.

KIMBALL, Evanston, Ill.

SOME ENDOCRINE FACTORS IN THE POLYURIC ACTION OF RENIN. H. CROXATTO, L. BARNAFI, L. CAMAZON, and V. PARRA, Endocrinology **54**:239 (March) 1954.

It has been shown that the injection of renin produces polyuria in rabbits and in rats. The polyuric effect of renin is abolished by adrenalectomy. Whether the adrenal factor involved in the action of renin arose from the cortex or from the medulla and whether or not it involved interaction with either the anterior or posterior pituitaries are questions left unanswered by past work. The present experiments were designed to provide such answers.

The results indicate that the polyuric action of renin is not due to a direct or indirect stimulation of the adrenal cortex; nor can the phenomenon be attributed to a temporary inhibition of the neurohypophysis, by decreasing antidiuretic hormone production. The adrenocortical hormones are, however, indispensable for the diuretic effect mentioned above. The essential and conditioning role of these hormones in the diuretic action of renin could be due to their reaction on the metabolism of Cl and Na, for the intensity of the diuretic effects of renin are markedly influenced by the ingestion of NaCl.

JACOBSEN, Buffalo.

STUDIES IN SPERM HORMONES: DEMONSTRATION OF ESTROGENIC ACTIVITY. C. A. SCHAFFENBURG and E. PERRY MCCULLAGH, with the assistance of D. C. TWEED, Endocrinology **54**:296 (March) 1954.

The mechanism by which the testes exert a regulatory influence on the anterior pituitary is still an obscure physiologic phenomenon. While large doses of testosterone may depress the pituitary gonadotropins, it is now generally agreed that physiologic quantities of this hormone do not inhibit the secretion of gonadotropin to a significant extent. This would indicate that either

there are other testicular hormones capable of inhibiting gonadotropins or that some other mechanism of pituitary control is involved.

In the experiments here reported estrogenic activity has been demonstrated in extracts prepared from bull sperm, which caused vaginal cornification and an increase in uterine weight in the spayed adult albino rat. The presence of estrogens in sperm, which may be considered a part of the testicular tubular epithelium, may explain some hitherto obscure phenomena in the control of the anterior pituitary by the testes.

JACOBSEN, Buffalo.

COMPARISON OF EFFECTS OF GONADECTOMY ON SPONTANEOUS ACTIVITY OF WILD AND DOMESTICATED NORWAY RATS. CURT P. RICHTER and E. H. UHLENHUTH, Endocrinology **54**:311 (March) 1954.

Gonadectomy greatly reduced the spontaneous activity of domesticated Norway rats but had little effect on the activity of wild Norways.

In explanation of the differences of the effects of gonadectomy in the two strains, it was suggested that the running activity of the wild rats is maintained largely by adrenal secretions, whereas the activity of domesticated rats is maintained largely by gonadal secretions. The results indicate that during the process of domestication of the Norway rat the gonads may have assumed the control of functions that are predominantly controlled by the adrenal in the wild state.

JACOBSEN, Buffalo.

MAINTENANCE OF BLOOD 17-HYDROXYCORTICOSTEROIDS FOLLOWING ASCORBIC ACID TREATMENT. HABEEB BACCHUS, Endocrinology **54**:402 (April) 1954.

It has been demonstrated that the eosinopenic and lymphopenic actions of exogenous and endogenous adrenocortical hormones are prolonged by ascorbic acid treatment. These data were interpreted as indicating that ascorbic acid in some manner maintains the circulating levels of these hormones. It was observed, also that simultaneous ascorbic acid treatment to adrenalectomized female rats receiving cortisone prevented the usual rise in the urinary 17-ketosteroids and permitted a significant increase in the corticosteroid excretion. These data were also supported by in vitro studies on liver slices, which indicated that ascorbic acid depresses the metabolism of cortical hormones.

This paper reports data on the effect of simultaneous ascorbic acid treatment on the circulating levels of 17-hydroxycorticosteroids in adrenalectomized rats injected with cortisone acetate.

It is suggested that ascorbate may depress the metabolism of cortical hormones.

JACOBSEN, Buffalo.

Cutaneous Diseases; Allergy

OFFICE MANAGEMENT OF ALLERGIC CHILDREN. MORTON ZALL, California Med. **82**:322 (April) 1955.

There is a high incidence of allergic disease in average pediatric practice. Proper diagnosis and treatment can and should be carried out by a higher percentage of practitioners. A thorough history is the most reliable diagnostic method. Skin testing is quite often a very necessary diagnostic tool. Following testing, desensitization may be necessary. The technical details of these procedures should be common medical knowledge. Where desensitization is necessary and is properly carried out, the results are definitely better than with mere symptomatic management.

PRYOR, Redwood City, Calif.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

PROTRUDED LUMBAR INTERVERTEBRAL DISKS IN CHILDREN. J. HUGH WEBB, H. J. SVIEN, and R. L. J. KENNEDY, J. A. M. A. **154**:1153 (April 3) 1954.

Only 5 of approximately 6500 patients who were operated on for protruded lumbar intervertebral disks were in children. Although rare in childhood, the occurrence of low backache and sciatic pain should suggest a ruptured disk. Myelography and removal of the lesion should be tried if conservative therapy has failed.

KIMBALL, Evanston, Ill.

MYASTHENIA GRAVIS IN EARLY CHILDHOOD. DONALD MACRAE, Pediatrics **13**:511 (June) 1954.

Four cases of myasthenia gravis in early childhood are reported. One case is congenital, and the infant exhibited no fetal movement, suggesting that the myasthenia had an intrauterine onset. The relationship of myasthenia to the coexisting maternal hyperthyroidism in the first case reported is considered in view of an apparent relationship in adults. That other "toxic" states may play a part is possible.

One of the children had a sister and possibly other siblings affected with myasthenia gravis. From the published accounts, it appears that a familial incidence of myasthenia is considerably higher in childhood. It is, however, concluded that this does not represent a genetic factor—rather that unknown environmental factors are operative.

Two children showed severe exacerbations during intercurrent infections—one being in complete remission between infections. The manner in which an infection results in an exacerbation is not clear.

The myasthenic-like state affecting the children of myasthenic mothers is discussed in relation to myasthenia. It is concluded from the evidence at present available that the defect in myoneural transmission in myasthenia gravis is the effect of a circulating substance whose nature, source, and mode of action remains obscure but appears to be continuously or intermittently secreted.

While myasthenia gravis is a rare disorder, it is becoming increasingly apparent that the incidence in early childhood is considerably higher than previously suspected. Some of the factors causing difficulty in diagnosis are discussed. FROM THE AUTHOR'S SUMMARY.

CONGENITAL COXA VARA: OSTEOCHONDRODYSPLASIA OF THE FEMORAL NECK. J. M. CLARK and G. M. JACOBSON, Radiology **63**:59 (July) 1954.

Congenital coxa vara of the hip is caused by osteochondrodysplasia of the femoral neck. A painless limp is the earliest symptom (4 to 12 years). Later there is shortening of the leg, with limitations of abduction and rotation. When the patient stands on the affected limb and lifts the opposite foot, the unaffected hip descends instead of rising. The diagnosis is dependent upon roentgenograms, which show the coxa vara deformity, shortening of the femoral neck, and often bony sclerosis. Subtrochanteric wedge osteotomy tends to prevent the shearing stress on the cartilaginous neck by overcorrecting the coxa vara deformity. This operation is the authors' choice of treatment. After this form of treatment, almost all cases have gone on to osseous union.

ANSPACH, Riverside, Ill.

NONRACHITIC BOWING OF THE TIBIA. ROBERT STEMPFEL, South. M. J. **47**:200 (March) 1954.

Twenty-four cases of nonrachitic bowing of the tibiae are reported. Equal division by sex was noted. None of the patients had any rachitic stigmata, though not all of them had determinations of calcium, phosphorus, or phosphatase content of the blood. Four had had apparently inadequate vitamin D intake. All were in a good state of nutrition. Onset of bowing was noted when infants were 6 to 12 months of age. The condition must be distinguished from rachitic bowing and osteochondritis deformans tibiae (Blount's Disease). Twelve cases were followed throughout the course of the disease. All of the infants showed complete regression without treatment.

LOGAN, Rochester, Minn.

CHONDROMYXOID FIBROMA. RICHARD N. WRENN and ALBERT G. SMITH, South. M. J. **47**:848 (Sept.) 1954.

This report of 5 cases brings the total of cases of this tumor reported in the literature to 13. The lesion occurs in older children and young adults more frequently than in older persons. It usually involves bones of the lower extremities. The course of the patients strongly suggests that such lesions are benign. Grossly the lesions are firm, uniformly resilient, and rubbery and can be easily separated from surrounding bone. Microscopically, they are found to consist of multipolar and spindle cells loosely embedded in a myxoid matrix. It is important that chondromyxoid fibroma not be confused with chondrosarcoma so that radical operative procedures can be avoided when the benign lesion is encountered.

LOGAN, Rochester, Minn.

EPIDERMOLYSIS BULLOSA IN THE NEWBORN. IAN C. LEWIS, ELUNED M. STEVEN, and JAMES W. FARQUHAR, Arch. Dis. Childhood **30**:277 (June) 1955.

Six cases are recorded of epidermolysis bullosa in infants. Three of them were the rare recessive form known as Herlitz disease; the other three were the dominant dystrophic variety.

The etiology, pathology, clinical features, and methods of treatment of the disease are discussed, and a table is given of the points for differential diagnosis of bullous eruptions in the newborn.

All cases of the Herlitz type and one of the others died. No abnormality of skin structure was found in the two cases of Herlitz disease which were examined after death.

KELLY, Milwaukee.

FOREARM FRACTURES IN CHILDHOOD. W. J. S. MELVIN, Canad. M. A. J. **70**:263 (March) 1954.

The commonest forearm fractures in childhood are of the rotational type. In most cases rotation in the opposite direction will produce accurate reductions.

McGUIGAN, Evanston, Ill.

ACUTE OSTEOMYELITIS AND SUPPURATIVE ARTHRITIS OF INFANTS. I. S. DE WET, South African M. J. **28**:81 (Jan. 30) 1954.

The author describes five cases of acute osteomyelitis and suppurative arthritis in infants. He considers this to be a separate entity because of the deceptively mild systemic effect and rapid local destruction as opposed to the usual course in older patients.

McGUIGAN, Evanston, Ill.

MILKMAN'S DISEASE. G. CAUDEDDU and P. RAVASIO, Ann. ital. pediat. **7**:129 (April) 1954.

The authors report Milkman's disease in two sisters and take it as a starting point for discussing the nosologic picture of the morbid form and for interpreting, after a careful examination of the literature, its etiopathogenetic factors, which, in their opinion, justify the viewpoint shared by other authors, that Milkman's syndrome is a form of osteopathy.

FROM THE AUTHORS' SUMMARY.

OSTEOCHONDRODYSTROPHY AND GROWTH. L. MARTONI and C. MONTANELLI, Clin. pediat. **36**:349 (May) 1954.

A 7-year-old boy, with a negative family history, was found to have a bilateral hip dislocation with restricted abduction, some shortening of the arms and legs (6 cm.) from normal, and a generalized loose-jointedness and to be easily fatigued on walking. X-ray examination revealed an abnormal development of both the diaphyses and the epiphyses. A diagnosis was made of a mild case of Morquio's disease without the familial characteristics, although the appearance of the child suggested a chondroplastic dwarfism.

HIGGINS, Boston.

CRANIOSTENOSIS. ROMAN ARANA IÑIGUEZ, MARÍA A. REBOLLO, EUCLIDES PELUFFO, ALFREDO U. RAMON GUERRA and LEANDRO RODRÍGUEZ MARTINICORENA, Arch. pediat. Uruguay **25**:461 (July) 1954.

A review of the etiopathogenesis, pathological anatomy, symptomatology, and treatment of craniostenosis is made. A lineal craniectomy was done in four patients, using the technique of Ingrahm and Matson.

FROM THE AUTHORS' SUMMARY.

BIOPHYSEAL STUDIES ON BONE TISSUE: III. OSTEOPETROSIS (MARBLE BONE DISEASE). B. ENGFELDT, A. ENGSTRÖM, and R. ZETTERSTRÖM, Acta paediat. **43**:152 (March) 1954.

In two cases of osteopetrosis the bone tissue has been studied by biophysical methods. The ultrastructure has been studied with x-ray diffraction and the distribution of mineral salts with microradiography; the molecular structure is the same as in normal bone. The distribution of the mineral salts is quite different from normal bones but shows characteristic patterns. The arrangement of collagen has been investigated in polarized light, the arrangement being quite irregular, a fact which seems to give a satisfactory explanation for the fragility of the bones. The cause of the diseases is to be found in some functional anomaly of the bone-forming cells.

FROM THE AUTHORS' SUMMARY.

Miscellaneous

RADIATION THERAPY IN PEDIATRICS. RALPH F. PHILLIPS, Am. J. Roentgenol. **74**:621 (Oct.) 1955.

This article discusses the problems encountered in evaluating the results of radiation therapy in children. Even though malignancy is third among the causes of death in children, it is nevertheless an uncommon disease, and statistical analyses of results with therapy are difficult to obtain.

There is an excellent discussion of the changing concepts of etiology and pathogenesis of tumors in children, and the tumor-host relationship is well illustrated by a number of examples.

Personal evaluation of radiosensitivity of normal and malignant tissue and effective tumor dose led to the conclusion that these factors were not directly related to the age of the patient.

The late effects of radiotherapy on growth and development are still largely unknown, and the necessity of particular care in treating nonmalignant lesions is again stressed.

ALTMAN, Miami, Fla.

INTRAMUSCULAR TERRAMYCIN: LABORATORY AND CLINICAL STUDIES IN CHILDREN. CHARLES O'REGAN and SIGMUND SCHWARZER, J. Pediat. **44**:172 (Feb.) 1954.

The authors gave intramuscular Terramycin to 45 children. Twenty per cent had some local irritation. The authors suggest that this might be avoided if the injections are given deeply into the gluteal muscles at 24-hour intervals, alternating the buttocks; the concentration should be 100 mg. per cubic centimeter. Many infants and young children tolerated the drug very well.

An intramuscular dose of 6 mg. per kilogram gives blood levels equal to a single oral dose of 22 or 33 mg. per kilogram. Higher levels can be obtained by increasing the intramuscular dose to 50 mg. per kilogram. Therapeutic levels can be obtained within 15 minutes after intramuscular administration, which indicates that intravenous therapy is not essential. No matter what the route of administration, Terramycin does not diffuse well to the cerebral spinal fluid.

The authors suggest that to inhibit Streptococcus pyogenes Group A, hemolytic Staphylococcus aureus, Hemophilus influenzae, and Neisseria gonorrhoeae, Terramycin, 6-12 mg. per kilogram for 24 hours, should be adequate. Urinary tract infections caused by Gram-negative Escherichia coli and Proteus vulgaris require a dose of 25 mg. per kilogram for 24 hours or more.

Since Terramycin is only bacteriostatic in lower concentrations, the authors recommend that the drug should be given in high concentrations at 12-hour intervals in order to produce a bactericidal effect in severely ill patients.

MACDONALD, Pittsburgh.

METHEMOGLOBINEMIA DUE TO THE ACUTE POISONING OF A CHILD BY ANILINE. G. ACETO and S. LI MOLI, Clin. pediat. **36**:243 (April) 1954.

A 10-year-old girl had applied a black liquid dye (containing aniline) to her cloth shoes, daubing her fingers in the process; she then put on her shoes, omitting stockings, and went to school. In about a half hour she complained of weakness and headache and was observed to be cyanotic and to have a rapid pulse; she was brought to the hospital. Spectrophotometric examination revealed about 3.30 gm. of methemoglobin per 100 cc. of blood. Treatment consisted of a clysis of 100 cc. 5% glucose containing 0.5 gm. of ascorbic acid, followed by an I. V. injection of 50 mg. of methylene blue in physiological salt solution. Four hours later the color of the child's skin and mucous membranes was normal. Twelve hours later, a spectrophotometric determination showed 0.45 gm. of methemoglobin per 100 cc. of blood.

HIGGINS, Boston.

THE DETERMINATION OF ISONIAZID IN THE SPINAL FLUID BY A BIOLOGICAL METHOD. G. CASCIO and R. PURPURA, Minerva pediat. **6**:101 (Feb. 15) 1954.

In patients with tuberculous meningitis, the speed of the passage of isoniazid administered orally or intramuscularly into the spinal fluid increases with the degree of meningeal inflammation; the maximum concentration in the spinal fluid is usually reached in three hours. When the drug is given intraspinally, its concentration falls quite rapidly below the bacteriostatic level; it is therefore advisable to supplement intraspinal injections by oral administration.

HIGGINS, Boston.

PYRAMIDON (AMINOPYRINE) AND THE SUPRARENAL CORTEX. B. FANTUZZI, Minerva pediat. **6**:333 (May 15) 1954.

Observations with Pyramidon on rheumatic fever patients, rabbits, and rats indicate that the drug causes pharmacological reactions similar to those caused by ACTH; there is a fall in the eosinophile count, an increase in the blood level of ascorbic acid, and an increase in uric acid excretion and usually in the excretion of androgens. Pyramidon is excreted from the body very rapidly and never reaches a high level in the blood.

HIGGINS, Boston.

PREVENTION OF OTITIS MEDIA IN SCARLET FEVER. G. MUNDY, Med. Klin. **50**:399 (March 11) 1955.

Methenamine (Urotropin) was given to children in a 1.5% solution t. i. d. to prevent otitis media, which did not occur any more following this medication. The number of cases is as yet too small and the observation too short to permit for reaching conclusions.

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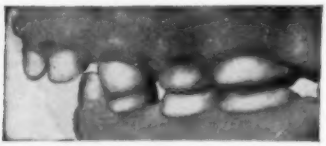

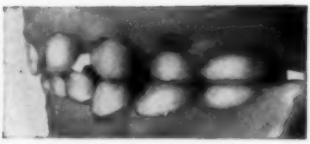

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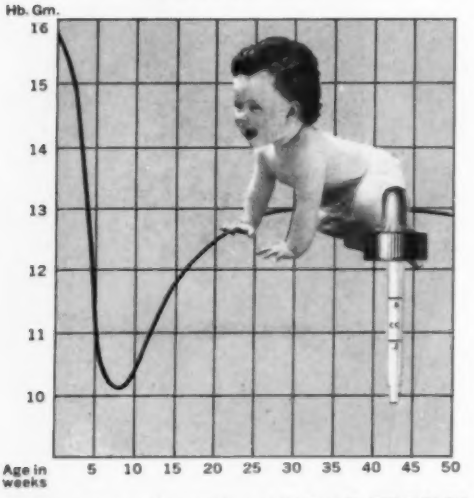

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(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 88: 553, 1953. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 156, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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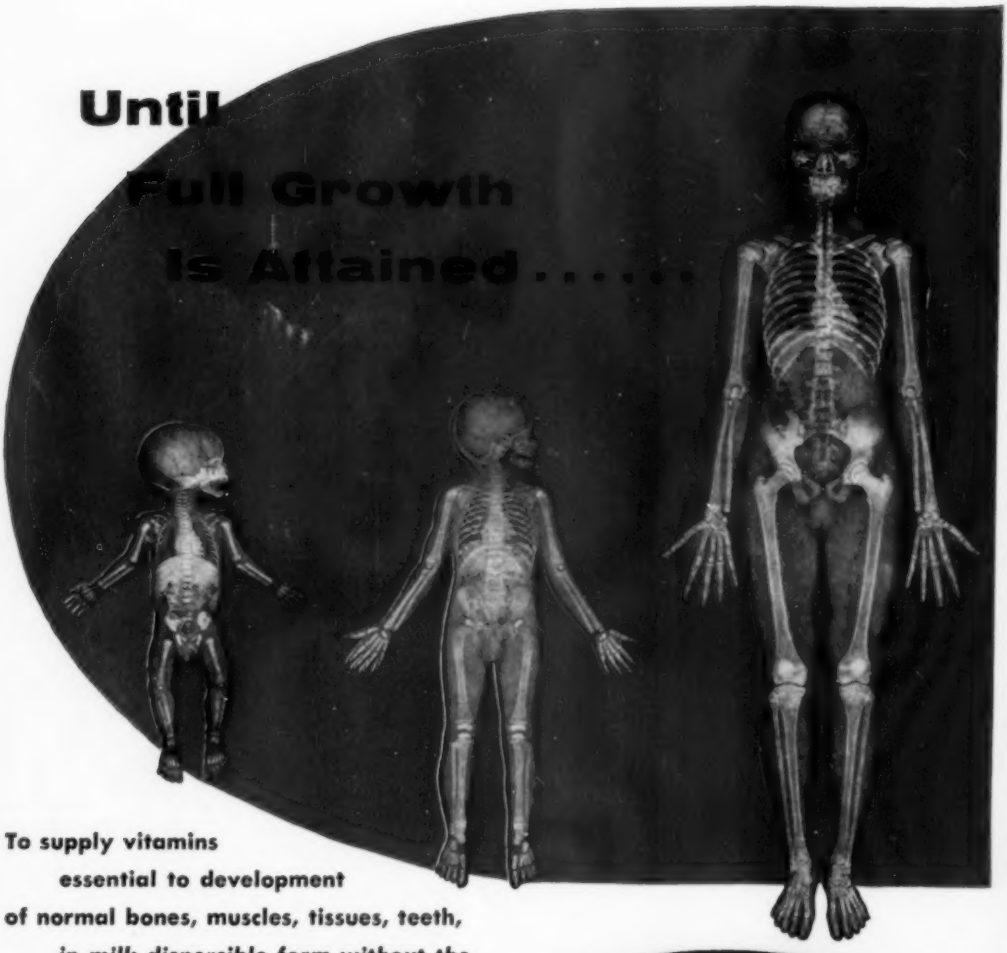

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